# WEST Search History

DATE: Monday, June 17, 2002

| Set Name side by side | Query | Hit Count | Set Name result set |
|---|---|---|---|
| *DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=OR* | | | |
| L12 | (chimeric)adj(IgE) | 31 | L12 |
| L11 | (IgE)adj(domain$)adj(fusion) | 0 | L11 |
| L10 | (non)adj(placental)adj(mammal)same(IgE) | 1 | L10 |
| L9 | (polypeptide)same((IgE)adj(CH3)adj(domain)) | 1 | L9 |
| L8 | (IgE)same((CH2)and(CH3)and(CH4)adj(domain$)) | 8 | L8 |
| *DB=USPT; PLUR=YES; OP=OR* | | | |
| L7 | (IgE)same((CH2)and(CH3)and(CH4)adj(domain$)) | 5 | L7 |
| L6 | (IgE)same(((CH1)and(CH2)and(CH3)and(CH4))adj(domain$)) | 2 | L6 |
| L5 | 5653980.pn. | 1 | L5 |
| *DB=USPT,DWPI; PLUR=YES; OP=OR* | | | |
| L4 | 9305810 | 8 | L4 |
| *DB=DWPI; PLUR=YES; OP=OR* | | | |
| L3 | wo9305810 | 0 | L3 |
| *DB=USPT; PLUR=YES; OP=OR* | | | |
| L2 | (IgE)same(CH2)adj(domain)same(CH3)adj(domain)same(CH4)adj(domain) | 3 | L2 |
| L1 | (chimeric)adj(IgE) | 26 | L1 |

END OF SEARCH HISTORY

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| NEWS 2 | | "Ask CAS" for self-help around the clock |
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| NEWS 21 | Feb 24 | METADEX enhancements |
| NEWS 22 | Feb 24 | PCTGEN now available on STN |
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| NEWS 31 | Apr 14 | MEDLINE Reload |
| NEWS 32 | Apr 17 | Polymer searching in REGISTRY enhanced |
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| NEWS 34 | Apr 21 | New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX |
| NEWS 35 | Apr 28 | RDISCLOSURE now available on STN |
| NEWS 36 | May 05 | Pharmacokinetic information and systematic chemical names added to PHAR |
| NEWS 37 | May 15 | MEDLINE file segment of TOXCENTER reloaded |
| NEWS 38 | May 15 | Supporter information for ENCOMPPAT and ENCOMPLIT updated |
| NEWS 39 | May 16 | CHEMREACT will be removed from STN |
| NEWS 40 | May 19 | Simultaneous left and right truncation added to WSCA |
| NEWS 41 | May 19 | RAPRA enhanced with new search field, simultaneous left and right truncation |
| NEWS 42 | Jun 06 | Simultaneous left and right truncation added to CBNB |
| NEWS 43 | Jun 06 | PASCAL enhanced with additional data |

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NEWS 44  Jun 20  2003 edition of the FSTA Thesaurus is now available
NEWS 45  Jun 25  HSDB has been reloaded

NEWS EXPRESS  April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
              MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
              AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
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FILE 'HOME' ENTERED AT 08:25:47 ON 10 JUL 2003

=> file medline embase biosis caplus scisearch
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=> s IgE chimera
L1            6 IGE CHIMERA

=> dup remove l1
PROCESSING COMPLETED FOR L1
L2            4 DUP REMOVE L1 (2 DUPLICATES REMOVED)

=> d l2 1-4 cbib abs

L2   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2003 ACS
1997:166948   Document No. 126:249957  The effect of intravenous administration
     of a chimeric anti-IgE antibody on serum IgE levels in atopic subjects:
     efficacy, safety, and pharmacokinetics.  Corne, Jonathan; Djukanovic,
     Ratko; Thomas, Lynette; Warner, Jane; Botta, Luigi; Grandordy, Beatrice;
     Gygax, Daniel; Heusser, Christoph; Patalano, Francesco; Richardson,
     William; Kilchherr, Erich; Staehelin, Theophil; Davis, Frances; Gordon,
     Wayne; Sun, Lee; Liou, Ruey; Wang, George; Chang, Tse-Wen; Holgate,
     Stephen (Southampton General Hospital, Univ. Med., Southampton, UK).
     Journal of Clinical Investigation, 99(5), 879-887 (English) 1997.  CODEN:
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JCINAO. ISSN: 0021-9738. Publisher: Rockefeller University Press.

AB CGP 51901 is a non-anaphylactogenic mouse/human chimeric anti-human IgE antibody that binds to free IgE and surface IgE of IgE-expressing B cells but not to IgE bound to high affinity IgE receptors (Fc.epsilon.R1) on mast cells and basophils or low affinity IgE receptors (Fc.epsilon.R2) on other cells. A phase 1 double-blind, placebo-controlled, single dose study with doses of 3, 10, 30, and 100 mg of CGP 51901 was conducted in 33 pollen-sensitive subjects who had raised levels of serum IgE and received either i.v. CGP 51901 or placebo. The administration of GCP 51901 was well tolerated and resulted in a decrease of serum free IgE levels in a dose-dependent manner, with suppression after 100 mg of CGP 51901 reaching > 96%. Time of recovery of 50% of baseline IgE correlated with the dose of administered antibody and ranged from a mean of 1.3 d for the 3 mg of 39 d for the 100 mg dose. Total IgE, comprised of free and complexed IgE, increased as stored and newly synthesized IgE bound to CGP 51901. Complexed IgE was eliminated at a rate comparable with the terminal half-life of free CGP 51901 (11-13 d at all doses). Only one subject showed a weak antibody response against CGP 51901. We conclude that the use of anti-human IgE antibody is safe and effective in reducing serum IgE levels in atopic individuals and provides a potential therapeutic approach to the treatment of atopic diseases.

L2 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2003 ACS

1997:302124 Document No. 126:329160 Production of a mouse/human chimeric IgE monoclonal antibody to the house dust mite allergen Der p 2 and its use for the absolute quantification of allergen-specific IgE. Schuurman, Janine; Perdok, Gerrard J.; Lourens, Tom E.; Parren, Paul W. H. I.; Chapman, Martin D.; Aalberse, Rob C. (Central Laboratory of the Netherlands Red Cross Blood Transfusion Service and Laboratory of Experimental and Clinical Immunology, University of Amsterdam, Amsterdam, Neth.). Journal of Allergy and Clinical Immunology, 99(4), 545-550 (English) 1997. CODEN: JACIBY. ISSN: 0091-6749. Publisher: Mosby-Year Book.

AB A chimeric human IgE monoclonal antibody was developed against the house dust mite allergen Der p 2. This chimeric antibody (hIgE-Dp2A) was composed of the heavy-chain variable domains and light chains of the original murine monoclonal antibody retaining its binding characteristics, whereas the heavy-chain const. domains were exchanged with the human IgE heavy chain. The chimeric IgE expression level was IgE 600 IU/mL (1 IU = 2.4 ng/mL). The binding of the chimeric hIgE-Dp2A to mite ext. was indistinguishable from that of the original mouse monoclonal antibody. Parallel dose-response curves were found when the binding of hIgE-Dp2A to mite ext. and anti-IgE coupled to sepharose were compared. Binding levels were not identical; however, hIgE-Dp2A bound significantly better to the mite-ext. sepharose. This result indicates that the commonly used anti-IgE on solid phase calibration systems may lead to an overestimation of the amt. of allergen-specific IgE present in the serum sample. The less efficient binding of the detector anti-IgE in case of the anti-IgE sepharose is likely to be because of the occupation of epitopes of the IgE by the sepharose-bound anti-IgE. Dose-response curves of serial dilns. of patient samples were parallel with the hIgE-Dp2A dose-response curve, which indicates that hIgE-Dp2A behaves like natural IgE antibodies in binding to allergen coupled to solid phase. This antibody is well suited for use as a ref. reagent in the RAST and enables the expression of the amt. of allergen-specific IgE present in a patient sample in abs. amts.

L2 ANSWER 3 OF 4 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 1

95336719 EMBASE Document No.: 1995336719. The use of mouse/human **IgE chimeras** to map the Fc.epsilon.R binding site of IgE. Nissim A.; Schwarzbaum S.; Eshhar Z.. Department of Chemical Immunology, Weizmann Institute of Sciences,Rehovot 76100, Israel. Methods: A Companion to Methods in Enzymology 8/2 (124-132) 1995.
ISSN: 1046-2023. CODEN: MTHDE. Pub. Country: United States. Language: English. Summary Language: English.

AB The binding of IgE antibodies to their specific receptors on mast cells is

a crucial step in the allergic response and can serve as a paradigm for the study of receptor-ligand interactions. Intense efforts have been made to identify amino acid sequences and structural motifs on the IgE molecule that may be involved in the binding to the Fc.epsilon. receptor. Studies using short IgE peptides or fragments are restricted by the conformation of these polypeptides, as a sequence that corresponds to the receptor-binding epitope on the IgE molecule may adopt a different, nonbinding conformation in solution. To avoid this difficulty, we have used exon shuffling between mouse and human IgE to identify the domain involved in binding to the mouse and human low- and high-affinity Fc.epsilon. receptors. The results obtained using such human-mouse **IgE chimeras** strongly suggest that the C.epsilon.3 domain is sufficient for species-specific binding to both the low- and the high-affinity Fc.epsilon. receptors. Binding is observed even upon deletion of the C.epsilon.2 domain. Within the C.epsilon.3 domain, conformational determinants composed of residues from throughout the domain are needed to form the binding site for the Fc.epsilon.RI. For the low-affinity receptor, the binding site appears to reside in the C-terminal part of C.epsilon.3.

L2 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS
1985:180102 Document No. 102:180102 A hapten-specific chimeric IgE antibody with human physiological effector function. Neuberger, M. S.; Williams, G. T.; Mitchell. E. B.; Jouhal, S. S.; Flanagan, J. G.; Rabbitts, T. H. (Lab. Mol. Biol., MRC, Cambridge, CB2 2QH, UK). Nature (London, United Kingdom), 314(6008), 268-70 (English) 1985. CODEN: NATUAS. ISSN: 0028-0836.
AB Recombinant plasmid DNA encoding human IgE heavy chain const. region and the mouse variable region was introduced by spheroplast fusion into mouse plasmacytoma J558L that secretes .lambda.1 light chains but does not produce an Ig heavy chain. The mouse cell line obtained secretes a chimeric IgE, .lambda.1 antibody whose heavy chain is composed of a human C.epsilon. const. region fused to a mouse variable (VH) region. This chimeric IgE is specific for the hapten 4-hydroxy-3-nitrophenacetyl [6322-56-1] and can, when crosslinked by antigen, trigger the degranulation of human basophils. When not crosslinked, however, the chimeric IgE can prevent the passive sensitization (histamine [51-45-6] release) of these cells by sera from allergic subjects.

=> s IgE fusion
L3 7 IGE FUSION

=> dup remove l3
PROCESSING COMPLETED FOR L3
L4 7 DUP REMOVE L3 (0 DUPLICATES REMOVED)

=> d l4 1-7 cbib abs

L4 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2003 ACS
2002:716299 Document No. 137:246549 Immunoglobulin fusion proteins that target low-affinity Fc.gamma. receptors. Arnason, Barry G. W.; Jensen, Mark A.; White, David M. (University of Chicago, USA). PCT Int. Appl. WO 2002072608 A2 20020919, 139 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US7365 20020311. PRIORITY: US 2001-PV274392 20010309.
AB The present invention concerns a family of nucleic acids, polypeptides and cloning vectors which direct expression of fusion proteins that can mimic

aggregated IgG (AIG) and immune complex function with respect to their interactions with Fc.gamma.R and which allow for the inclusion and targeting of a second protein domain to cells expressing Fc.gamma.R. This was accomplished by expressing multiple linear copies of the hinge and CH2 domains (HCH2) of human IgG1 fused to the Fc region of human IgG1. Convenient restriction sites allow for the facile introduction of addnl. N-terminal domains. In one example, the extracellular domain of human CD8.alpha. was fused with 0-4 HCH2 segments and the Fc region of IgG1. The fusion protein was shown to stimulate proliferation of interleukin-2-primed natural killer cells.

L4 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2003 ACS

2001:50815 Document No. 134:130249 Fc.epsilon. receptor fusions with chemi- or bioluminescence-inducing proteins and their uses in IgE detection. Weber, Eric R.; Wood, Keith V.; Hall, Mary P. (Heska Corporation, USA; Promega Corporation). PCT Int. Appl. WO 2001004310 A1 20010118, 104 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US19070 20000713. PRIORITY: US 1999-PV143612 19990713; US 2000-PV186412 20000302.

AB The present invention relates to chimeric genes for Fc.epsilon. receptor fused to bioluminescence- or chemiluminescence-inducing proteins, fusion proteins encoded by such nucleic acid mols., and methods of using such proteins and nucleic acid mols. for the detection of IgE and for identifying compds. capable of inhibiting Fc.epsilon. receptor activity. Thus, chimeric genes encoding human Fc.epsilon. receptor extracellular domain fused to luciferase or alk. phosphatase were constructed and expressed in Escherichia coli. These fusion proteins were used in detection of anti-flea saliva antigen or anti-Dermatophagoides pteronyssinus antigen IgE in allergy patients' sera.

L4 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2003 ACS

1998:178127 Document No. 128:214189 Recombinant protein expression and secretion by mammalian host cell using mammalian signal sequence and immunoglobulin Fc region fusion with target protein (immunofusins). Lo, Kin-ming; Sudo, Yukio; Gillies, Stephen D. (Fuji ImmunoPharmaceuticals Corp., USA). U.S. US 5726044 A 19980310, 18 pp., Cont.-in-part of U.S. 5,541,087. (English). CODEN: USXXAM. APPLICATION: US 1995-528122 19950914. PRIORITY: US 1994-305700 19940914.

AB Disclosed are DNAs produced by recombinant techniques for inducing the expression and subsequent secretion of a target protein. The DNAs encode, in their 5' to 3' direction, a secretion cassette, including a signal sequence and an Ig Fc region, and a target protein. The DNAs can be transfected into a host cell for the expression, prodn. and subsequent secretion of the target protein as a fusion protein. The secreted protein can be collected from the extracellular space, and further purified as desired. The secreted fusion protein addnl. can be proteolytically cleaved to release the target protein from the secretion cassette. An exemplary secretion cassette comprises the signal sequence of an Ig light chain of the 14.18 antibody modified for ease of cloning, the Fc region of human Fc.gamma.1 genomic DNA (including the genomic configuration of the hinge, CH2 and CH3 regions), a proteolytic cleavage site-encoding sequence, and DNA sequences encoding target proteins such as CD26, interleukin-2, HIV Tat or Rev proteins, OSF-2 secretory protein involved in ossification, etc.

L4 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2003 ACS

1996:350365 Document No. 125:27685 Recombinant protein expression and secretion by mammalian host cell using mammalian signal sequence and immunoglobulin Fc region fusion with target protein. Lo, Kin-Ming; Sudo,

Yukio; Gillies, Stephen D. (Fuji Immunopharmaceuticals Corporation, USA). PCT Int. Appl. WO 9608570 A1 19960321, 51 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1995-US11720 19950914. PRIORITY: US 1994-305700 19940914.

AB Disclosed are DNAs produced by recombinant techniques for inducing the expression and subsequent secretion of a target protein. The DNAs encode, in their 5' to 3' direction, a secretion cassette, including a signal sequence and an Ig Fc region, and a target protein. The DNAs can be transfected into a host cell for the expression, prodn. and subsequent secretion of the target protein as a fusion protein. The secreted protein can be collected from the extracellular space, and further purified as desired. The secreted fusion protein addnl. can be proteolytically cleaved to release the target protein from the secretion cassette.

L4 ANSWER 5 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

1994:46608 Document No.: PREV199497059608. High level expression and characterization of a recombinant CD4-**IgE-fusion** protein. Kufer, P.; Krauss, S.; Person, S.; Federle, C.; Rieber, E. P.; Riethmueller, G.. Inst. Immunol., Muenchen Germany. Immunobiology, (1993) Vol. 189, No. 1-2, pp. 228. Meeting Info.: 24th Meeting of the Society for Immunology Leipzig, Germany September 30-October 2, 1993 ISSN: 0171-2985. Language: English.

L4 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2003 ACS

1990:49998 Document No. 112:49998 Cloning and expression of cDNA for soluble CD4 derivatives and fusion proteins. Capon, Daniel J.; Gregory, Timothy J. (Genentech, Inc., USA). Eur. Pat. Appl. EP 314317 A1 19890503, 36 pp. DESIGNATED STATES: R: ES, GR. (English). CODEN: EPXXDW. APPLICATION: EP 1988-309194 19881003. PRIORITY: US 1987-104329 19871002; US 1988-250785 19880928.

AB Water-sol. derivs. of the CD4 antigen and water-sol. fusions of CD4 with Ig polypeptides that are potentially useful as therapeutic agents are described. A series of CD4-herpesvirus glycoprotein D fusion proteins were prepd. and their interaction with human immunodeficiency virus (HIV) gp120 studies. Binding consts. for the interaction were .apprx.10-9M. The sol. fusion proteins also greatly reduced the infection of culture cells by HIV.

L4 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2003 ACS

1986:220129 Document No. 104:220129 Production of immunogleukin EC22 by transformed Escherichia coli. Senoo, Masaharu; Onda, Haruo; Igarashi, Koichi (Takeda Chemical Industries, Ltd. , Japan). PCT Int. Appl. WO 8504673 A1 19851024, 36 pp. DESIGNATED STATES: W: MC. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1984-JP181 19840410.

AB A recombinant DNA is produced by ligating a DNA fragment that encodes an antibody recognition site (e.g., IgE) with a DNA fragment that encodes a human interleukin 2 (HIL-2). Escherichia coli Transformed with a plasmid contg. the recombinant DNA produces a polypeptide consisting of the human IgE and human IL-2 called immunogleukin EC22 (IGL-EC22). Thus, plasmid pGEL1028 was constructed by ligating an 8-kilobase (kb) DNA fragment contg. the gene encoding the C2 region of the human IgE heavy chain, which was isolated from the E. coli plasmid pGETtrp818-C, with a 500-kb DNA fragment contg. the gene for HIL-2 from E. coli plasmid pTF1. E. coli Were transformed with plasmid IGL-EC22. The nucleotide sequence, its encoded amino acid sequence, and a restriction map of the recombinant DNA are given. The product immunogleukin EC22 is a useful reagent for purifn. of human interleukin 2 antibody.

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=> s IgE domain
L5          22 IGE DOMAIN

=> s l5 and CH2
L6           0 L5 AND CH2
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=> dup remove l5
PROCESSING COMPLETED FOR L5
L7 15 DUP REMOVE L5 (7 DUPLICATES REMOVED)

=> d l7 1-15 cbib abs

L7 ANSWER 1 OF 15 CAPLUS COPYRIGHT 2003 ACS
2002:439831 Document No. 137:61769 Generation of therapeutic antibody responses against IgE through vaccination. Vernersson, Molly; Ledin, Anna; Johansson, Jeannette; Hellman, Lars (Department of Cell and Molecular Biology, Biomedical Center, University of Uppsala, Uppsala, S-751 24, Swed.). FASEB Journal, 16(8), 875-877, 10.1096/fj.01-0879fje (English) 2002. CODEN: FAJOEC. ISSN: 0892-6638. Publisher: Federation of American Societies for Experimental Biology.
AB IgE is the central mediator in atopic allergies such as hay fever, eczema, and asthma; therefore, it is a prime target in the development of allergen-independent preventive treatments. We describe an active immunization strategy that has the potential to reduce IgE to a clin. significant extent. The active vaccine component is a chimeric IgE mol., C.vepsiln.2-C.vepsiln.3-C.vepsiln.4. The receptor-binding target domain, C.vepsiln.3, is derived from the recipient species, whereas the flanking domains, C.vepsiln.2 and C.vepsiln.4, are derived from an evolutionarily distant mammal. The flanking domains have dual functions, acting both as structural support for the C.vepsiln.3 domain and to break T cell tolerance by providing foreign T cell epitopes. The efficacy of the vaccine was studied in an ovalbumin-sensitized rat model. Vaccination resulted in antibody responses against IgE in all rats and in a substantial redn. in serum IgE levels in three out of four strains. The skin reactivity upon allergen challenge was significantly reduced in vaccinated animals. The vaccine appears to be safe to use as an antigen. No crosslinking activity was obsd. in sera of vaccinated animals, and the response to vaccination was reversible with time. Our results suggest that active immunization against IgE has the potential to become a therapeutic method for humans.

L7 ANSWER 2 OF 15 SCISEARCH COPYRIGHT 2003 THOMSON ISI
2000:179917 The Genuine Article (R) Number: 288GP. A soluble fibroblast growth factor receptor is released from HL-60 promyelocytic leukemia cells: Implications for paracrine growth control. Wang J F; Shen M; Fong G H; Hill D J (Reprint). UNIV WESTERN ONTARIO, ST JOSEPHS HLTH CTR, LAWSON RES INST, MED RES COUNCIL, LONDON, ON N6A 4V2, CANADA (Reprint); UNIV WESTERN ONTARIO, ST JOSEPHS HLTH CTR, LAWSON RES INST, MED RES COUNCIL, LONDON, ON N6A 4V2, CANADA; UNIV WESTERN ONTARIO, DEPT MED, LONDON, ON N6A 5O5, CANADA; UNIV WESTERN ONTARIO, DEPT PAEDIAT, LONDON, ON N6A 5O5, CANADA; UNIV WESTERN ONTARIO, DEPT BIOCHEM, LONDON, ON N6A 5O5, CANADA; UNIV WESTERN ONTARIO, DEPT PHYSIOL, LONDON, ON N6A 5O5, CANADA. GROWTH FACTORS (MAR 2000) Vol. 17, No. 3, pp. 203-&. Publisher: HARWOOD ACAD PUBL GMBH. C/O STBS LTD, PO BOX 90, READING RG1 8JL, BERKS, ENGLAND. ISSN: 0897-7194. Pub. country: CANADA. Language: English.
*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB The biological activities of fibroblast growth factors (FGF) are mediated by specific cell membrane receptors (FGFR), which have three immunoglobulin-like IgG domains in the extracellular region, The carboxy-terminal segment of the third **Ige domain** of FGFR1 could be encoded by different exons, designated IIIa, IIIb, or IIIc, While exons IIIb or IIIc encode receptor forms with both intracellular and extracellular domains, the FGF receptor becomes potentially a secreted form lacking the intracellular domain and the transmembrane region when exon IIIa is expressed. Using reverse transcription polymerase chain reaction, me have found that mRNAs encoding the nucleotide sequences of FGFR1-IIIa and FGFR1-IIIc are expressed in HL-60 cells. FGFR1-IIIa fragment mas synthesized by a glutathione S-transferase gene fusion system. The purified 33 kDa FGFR1-IIIa fragment fusion protein could bind [I-125]-labelled FGF-2 in Western Ligand blot analysis. Three species of

proteins with the molecular weights of 82, 60, and 50 kDa mere identified in serum-free, conditioned medium from HL-60 cells by Western blot using an antiserum against purified FGFR1-IIIa fragment fusion protein, Exposure to FGF-2 caused an increase in [H-3]-thymidine incorporation into DNA of HL-60 cells and increased cell proliferation, but the addition of FCFR1-IIIa fragment fusion protein inhibited FGF-2-stimulated DNA synthesis and caused a dose-dependent inhibition of FGF-2-stimulated cell proliferation, The effects on DNA synthesis were partly reversed by antibody against the FGFR1-IIIa fragment, These results indicate that both cell membrane spanning and secreted FGF receptors are expressed in HL-60 cells, and that the actions of FGFs as paracrine growth factors could be modulated by secreted FGF receptor forms.

L7 ANSWER 3 OF 15 CAPLUS COPYRIGHT 2003 ACS

1999:605476 Document No. 132:164865 Domain mapping and comparative binding features of eight dog IgE-specific reagents in ELISA, immunoblots, and immunohistochemistry. Griot-Wenk, M. E.; Marti, E.; DeBoer, D. J.; de Weck, A. L.; Lazary, S. (Division of Immunogenetics, Institute of Animal Breeding, Switz.). Veterinary Immunology and Immunopathology, 70(1,2), 117-124 (English) 1999. CODEN: VIIMDS. ISSN: 0165-2427. Publisher: Elsevier Science B.V..

AB Eight dog IgE-specific reagents including monoclonal and polyclonal antibodies (Ab) and a cross-reactive alpha chain of the human high affinity IgE receptor were mapped to recombinant fragments of the second (IgEf2) and third/fourth (IgEf3/4) domains of the dog IgE heavy chain. In ELISA, five out of eight reagents reacted to solid-phase bound IgEf2, of which two polyclonal Ab bound in addn. to IgEf3/4. All Ab which recognized at least one recombinant IgE fragment, also bound to IgE in ELISA, immunoblots, and immunohistochem. In contrast, only one monoclonal Ab, that did not bind to the recombinant IgE fragments, reacted with immunoblots of serum and immunohistochem. The alpha chain could only be applied to ELISA with serum IgE. Furthermore, there was a wide range of heat-lability of binding reactions. Comparative anal. of available dog IgE-specific reagents enables more in-depth functional studies on IgE-mediated phenomena in dogs, and helps to further establish the dog as an animal model for allergy research.

L7 ANSWER 4 OF 15 CAPLUS COPYRIGHT 2003 ACS

1994:628647 Document No. 121:228647 The binding site on human immunoglobulin E for its high affinity receptor. Presta, Leonard; Shields, Robert; O'Connell, Lori; Lahr, Steven; Porter, James; Gorman, Cornelia; Jardieu, Paula (Dep. Protein Eng., Genentech Inc., South San Francisco, CA, 94080, USA). Journal of Biological Chemistry, 269(42), 26368-73 (English) 1994. CODEN: JBCHA3. ISSN: 0021-9258.

AB IgE antibodies mediate allergic responses by binding to specific high affinity receptors, Fc.epsilon.RI, on mast cells and basophils. Previous studies have shown that the principal Fc.epsilon.RI binding site is located on the third const. domain, Fc.epsilon.3, of IgE. Based on a model of the IgE Fc.epsilon.3 (which is homologous to the second const. domain of IgG), homol. scanning mutagenesis and replacement of individual residues were used to det. the specific amino acids of human IgE involved in binding to human Fc.epsilon.RI. The amino acids are localized in 3 loops, which form a putative ridge on the most exposed side of the Fc.epsilon.3 domain of IgE and include Arg-408, Ser-411, Lys-415, Glu-452, Arg-465, and Met-469. The preponderance of charged residues suggests that IgE-Fc.epsilon.RI binding is mediated primarily by electrostatic interaction. Furthermore, it is possible to confer Fc.epsilon.RI binding to an IgG mol. by introducing these 3 IgE loops into the IgG C.gamma.2 domain.

L7 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2003 ACS

1994:678478 Document No. 121:278478 Domain-specific anti-IgE antibodies interfere with IgE binding to Fc.epsilon.RII. Miescher, Sylvia; Vogel, Monique; Stampfli, Martin R.; Wasserbauer, Erich; Kricek, Franz; Vorburger, Stefan; Stadler, Beda M. (Institute Clinical Immunology,

Inselspital, Bern, CH-3010, Switz.). International Archives of Allergy and Immunology, 105(1), 75-82 (English) 1994. CODEN: IAAIEG. ISSN: 1018-2438.

AB Human anti-IgE autoantibodies have been identified and implicated in the regulation of IgE-mediated reactions and IgE synthesis. To study the potential regulatory role of anti-IgE antibodies on IgE binding to the Fc.epsilon.RII the authors used a panel of IgE-specific monoclonal antibodies that were mapped by Western blotting against a series of recombinant .epsilon. domain peptides. Antibodies specific for all .epsilon. domains were detected except those against C.epsilon.H1. Using a competitive inhibition cell-binding assay on Fc.epsilon.RII + 8866 cells, the authors identified two major patterns of anti-IgE activity. Antibodies specific for the C.epsilon.H3 domain removed IgE whereas those specific for the C.epsilon.H2 domain enhanced IgE binding to the Fc.epsilon.RII. The anti-C.epsilon.H2 antibodies, in contrast to the anti-C.epsilon.H3 antibodies, could not dissoc. cell-bound IgE from the Fc.epsilon.RII. Using preformed immune complexes of IgE and anti-IgE antibodies, it was clear that the anti-C.epsilon.H2 antibodies bound more IgE to the Fc.epsilon.RII by addn. of immune complexes to the cell surface. The results suggest that the opposing actions of either inhibition or enhancement of IgE binding by anti-IgE antibodies are related to their .epsilon. domain specificity.

L7 ANSWER 6 OF 15 MEDLINE DUPLICATE 1

93163561 Document Number: 93163561. PubMed ID: 7679426. Fine specificity of the IgE interaction with the low and high affinity Fc receptor. Nissim A; Schwarzbaum S; Siraganian R; Eshhar Z. (Department of Chemical Immunology, Weizmann Institute of Science, Rehovot, Israel. ) JOURNAL OF IMMUNOLOGY, (1993 Feb 15) 150 (4) 1365-74. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The characterization of the site(s) on the IgE molecule that accommodate the high (Fc epsilon RI) and low (Fc epsilon RII) affinity receptors for IgE should allow the design of IgE analogues that can be used to block the onset of the allergic response or to regulate IgE production. To identify the **IgE domain** responsible for receptor binding, we generated a series of chimeric IgE antibodies in which constant region domains were interchanged between the human and mouse molecules. Binding studies with these chimeras revealed that both the high and low affinity receptor binding-sites reside primarily in the third constant domain of IgE (C epsilon 3). Additional chimeric IgE molecules were generated in which different parts of the human C epsilon 3 domain were exchanged with their murine homologues. Binding experiments with these chimeras suggest that not only the sequence of a particular C epsilon 3 fragment, but the entire C epsilon 3 domain in its native configuration is essential for binding to the Fc epsilon RI. The amino acid residues determining the species specificity of the Fc epsilon RII are not contained in the first 16 amino acids of the C epsilon 3 domain.

L7 ANSWER 7 OF 15 CAPLUS COPYRIGHT 2003 ACS

1992:549197 Document No. 117:149197 The human mast cell receptor binding site maps to the third constant domain of immunoglobulin E. Nissim, Ahuva; Eshhar, Zelig (Dep. Chem. Immunol., Weizmann Inst. Sci., Rehovot, 76100, Israel). Molecular Immunology, 29(9), 1065-72 (English) 1992. CODEN: MOIMD5. ISSN: 0161-5890.

AB The characterization of the site on the IgE mol. which accommodates the high affinity receptor for IgE (Fc.epsilon.RI) should allow the design of IgE analogs which can be utilized to block allergic responses. Using chimeric human IgE mols. in which different const. region domains were exchanged with their murine homologs, the authors demonstrate that the C.epsilon.3 in its native configuration is essential for the binding to the .alpha. subunit of the human Fc.epsilon.RI. Deletion of the human C.epsilon.2 from such chimeric mols. did not impair their ability to interact with the Fc.epsilon.RI, indicating that C.epsilon.2 is not directly involved in the human Fc.epsilon.RI binding site and that C.epsilon.3 alone is necessary and sufficient to account for most of the

human Fc.epsilon.RI-binding capacity.

L7 ANSWER 8 OF 15 MEDLINE DUPLICATE 2
91114691 Document Number: 91114691. PubMed ID: 1824934. Mapping of the high affinity Fc epsilon receptor binding site to the third constant region domain of IgE. Nissim A; Jouvin M H; Eshhar Z. (Department of Chemical Immunology, Weizmann Institute of Science, Rehovot, Israel. ) EMBO JOURNAL, (1991 Jan) 10 (1) 101-7. Journal code: 8208664. ISSN: 0261-4189. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Identification of the precise region(s) on the IgE molecule that take part in the binding of IgE to its high affinity receptor (Fc epsilon RI) may lead to the design of IgE analogues able to block the allergic response. To localize the Fc epsilon RI-binding domain of mouse IgE, we attempted to confer on human IgE, which normally does not bind to the rodent receptor, the ability to bind to the rat Fc epsilon RI. Employing exon shuffling, we have expressed chimeric epsilon-heavy chain genes composed of a mouse (4-hydroxy-3-nitrophenyl)acetic acid (NP)-binding VH domain, and human C epsilon in which various domains were replaced by their murine counterparts. This has enabled us to test the Fc epsilon RI-binding of each mouse **IgE domain** while maintaining the overall conformation of the molecule. All of the chimeric IgE molecules which contain the murine C epsilon 3, bound equally to both the rodent and human receptor, as well as to monoclonal antibodies recognizing a site on IgE which is identical or very close to the Fc epsilon RI binding site. Deletion of the second constant region domain did not impair either the binding capacity of the mutated IgE or its ability to mediate mast cell degradation. These results assign the third epsilon domain of IgE as the principal region involved in the interaction with the Fc epsilon RI.

L7 ANSWER 9 OF 15 SCISEARCH COPYRIGHT 2003 THOMSON ISI
91:57911 The Genuine Article (R) Number: EU787. MAPPING OF THE HIGH-AFFINITY FC-EPSILON RECEPTOR-BINDING SITE TO THE 3RD CONSTANT REGION DOMAIN OF IGE. NISSIM A (Reprint); JOUVIN M H; ESHHAR Z. WEIZMANN INST SCI, DEPT CHEM IMMUNOL, IL-76100 REHOVOT, ISRAEL (Reprint); NIAID, MOLEC ALLERGY & IMMUNOL SECT, ROCKVILLE, MD, 20852. EMBO JOURNAL (1991) Vol. 10, No. 1, pp. 101-107. Pub. country: ISRAEL; USA. Language: ENGLISH.
*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB Indentification of the precise region(s) on the IgE molecule that take part in the binding of IgE to its high affinity receptor (Fc-epsilon-RI) may lead to the design of IgE analogues able to block the allergic response. To localize the Fc-epsilon-RI-binding domain of mouse IgE, we attempted to confer on human IgE, which normally does not bind to the rodent receptor, the ability to bind to the rat Fc-epsilon-RI. Employing exon shuffling, we have expressed chimeric epsilon-heavy chain genes composed of a mouse (4-hydroxy-3-nitrophenyl)acetic acid (NP)-binding V(H) domain, and human C-epsilon in which various domains were replaced by their murine counterparts. This has enabled us to test the Fc-epsilon-binding of each mouse **IgE domain** while maintaining the overall conformation of the molecule. All of the chimeric IgE molecules which contain the murine C-epsilon-3, bound equally to both the rodent and human receptor, as well as to monoclonal antibodies recognizing a site on IgE which is identical or very close to the Fc-epsilon-RI binding site. Deletion of the second constant region domain did not impair either the binding capacity of the mutated IgE or its ability to mediate mast cell degradation. These results assign the third epsilon domain of IgE as the principal region involved in the interaction with the Fc-epsilon-RI.

L7 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2003 ACS
1989:229778 Document No. 110:229778 The B-cell binding site on human immunoglobulin E. Vercelli, Donata; Helm, Birgit; Marsh, Philip; Padlan, Eduardo; Geha, Raif S.; Gould, Hannah (Div. Immunol., Children's Hosp., Boston, MA, 02115, USA). Nature (London, United Kingdom), 338(6217), 649-51 (English) 1989. CODEN: NATUAS. ISSN: 0028-0836.
AB Peptide and monoclonal antibody studies show that the Fc.epsilon. receptor

2 of B lymphocytes can recognize a motif in the IgE C.epsilon.3 domain near the Lys 367-Val 370 region. Glycosylation of IgE is not required for receptor activity.

L7 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2003 ACS
1987:475759 Document No. 107:75759 Analysis of the interaction between rat immunoglobulin E and rat mast cells using anti-peptide antibodies. Burt, David S.; Hastings, Gillian Z.; Healy, John; Stanworth, Denis R. (Dep. Immunol., Univ. Birmingham, Birmingham, B15 2TJ, UK). Molecular Immunology, 24(4), 379-89 (English) 1987. CODEN: MOIMD5. ISSN: 0161-5890.
AB Polyclonal antisera with predetd. specificities for a range of rat IgE epitopes were produced by immunizing rabbits with keyhole limpet hemocyanin-conjugates of 5 different synthetic peptides representing sequences 378-396, 414-428, 491-503, 522-535 and 560-571 in the CH3 and CH4 domains of rat IgE. Each rabbit elicited peptide-specific antibodies which were capable of binding affinity-purified rat IgE and IgE in rat immunocytoma serum. Heating a soln. of rat IgE at 56.degree. for 1 h, a treatment known to abolish the cytophilic activity of rat IgE and also induce irreversible conformational changes in the CH3 and CH4 domains, resulted in enhanced binding of the Ig to antibodies directed against IgE sequences represented by 2 of the synthetic peptides, 414-428 and 491-503, but not to the 3 other peptides. The 5 anti-peptide sera together with 2 previously studied antisera specific for rat IgE sequence 459-472 and 542-557 were tested in functional assays designed to investigate the mode of interaction between rat IgE and its receptor on rat mast cells. Each anti-peptide serum was capable of inhibiting the binding of IgE to mast cells and able to initiate the secretion of histamine from cells sensitized with rat IgE in an anti-IgE-induced manner. Based on the evidence implicating the CH3 and/or CH4 domains as the location of the mast cell receptor-site on rat IgE, a model to describe the mode of interaction between IgE and its mast cell receptor is suggested.

L7 ANSWER 12 OF 15 CAPLUS COPYRIGHT 2003 ACS
1986:205156 Document No. 104:205156 Thermoinactivation of human IgE: antigenic and functional modifications. Demuelemester, C.; Weyer, A.; Peltre, G.; Laurent, M.; Marchand, F.; David, Bernard (Lab. Immuno-Allergie, Inst. Pasteur, Paris, 75724/15, Fr.). Immunology, 57(4), 617-20 (English) 1986. CODEN: IMMUAM. ISSN: 0019-2805.
AB The thermoinactivation kinetics of IgE were studied in exptl. models revealing the antigenic properties and the basophil-sensitizing capacity of these Igs. A pool of human sera contg. anti-Dactylis glomerata (Dg) IgE was heated from 5 min up to 4 h at 56.degree.. The IgE antigenicity was tested by 2 polyclonal 125I-labeled anti-IgE antibodies; one anti-IgE was specific of the whole Fc.epsilon. region, while the other had a specificity restricted to the D.epsilon.2 domain. Radioimmunoassays showed that the D.epsilon.2 epitopes were more rapidly altered than the D.epsilon.1 epitopes. The capacity of IgE to bind to basophil Fc.epsilon. receptors was assayed by passive sensitization expts. Basophil sensitivity towards the Dg pollen ext. was tested by histamine release expts. in the presence of this allergen. A progressive decrease in cell sensitivity was obsd. when IgE samples used for cell sensitization were heated for >5 min. Thermoinactivation kinetics of IgE revealed an unexpected increase in the apparent quantity and biol. activity of IgE heated for 5 min at 56.degree.. This could be due to auto-anti-IgE antibodies linked to the unheated IgE which interfere with the biol. activities of IgE and their quantification.

L7 ANSWER 13 OF 15 CAPLUS COPYRIGHT 2003 ACS
1986:184529 Document No. 104:184529 Use of synthetic peptides in the production and characterization of antibodies directed against predetermined specificities in rat immunoglobulin E. Burt, David S.; Hastings, Gillian Z.; Stanworth, Denis R. (Dep. Immunol., Univ. Birmingham, Birmingham, B15 2TJ, UK). Molecular Immunology, 23(2), 181-91 (English) 1986. CODEN: MOIMD5. ISSN: 0161-5890.

AB Two peptides, P123 and P124, representing amino acid sequences His 542-Lys 557 and Tyr 459-Arg 472, resp., of the CH4 domain of rat IgE and predicted to be located on accessible regions of the protein were synthesized by a solid-phase procedure. Rabbits were immunized with the peptides conjugated to keyhole limpet hemocyanin and their antisera were tested for reactivity with free peptide and rat IgE by inhibition-ELISA. Each animal produced antibodies which reacted specifically with its immunizing peptide, but not with other synthetic peptides of similar chain-length and compn. Antisera directed against peptides P123 and P124 specifically bound purified rat IgE (IR 162) and IgE in whole myeloma serum, but showed no reaction with normal rat serum proteins and only very low binding to purified human IgE. In addn. the binding of anti-peptide sera to rat IgE was completely inhibited with either homologous peptide or purified rat IgE, but not by other peptides or purified human IgE. Heating rat IgE for 1 h at 56.degree. enhanced its binding to anti-peptide antibodies 4-60-fold, but markedly reduced its reactivity with a rabbit anti-rat IgE (Fc) serum. These results suggest that antibodies directed against the synthetic peptides recognize and specifically bind to sites within the CH4 domain of rat IgE represented by their resp. immunizing peptides. Furthermore, these antibodies are capable of detecting subtle alterations in structural conformation resulting from heating at 56.degree.. Epitopes represented by peptides P123 and P124 may contribute to the heat-sensitive cytophilic region of rat IgE.

L7 ANSWER 14 OF 15 CAPLUS COPYRIGHT 2003 ACS

1983:420734 Document No. 99:20734 Structural studies on the membrane-bound immunoglobulin E-receptor complex. 1. Characterization of large plasma membrane vesicles from rat basophilic leukemia cells and insertion of amphipathic fluorescent probes. Holowka, David; Baird, Barbara (Dep. Chem., Cornell Univ., Ithaca, NY, 14853, USA). Biochemistry, 22(14), 3466-74 (English) 1983. CODEN: BICHAW. ISSN: 0006-2960.

AB In order to investigate the properties of the membrane-bound IgE-receptor complex, a single procedure has been adapted for prepg. large plasma membrane vesicles from rat basophilic leukemia cells. These vesicles pinch off from the adherent cells after treatment with 2 mM N-ethylmaleimide or 50 mM formaldehyde and 1 mM dithiothreitol, and they are isolated from the supernatant after 2 centrifugation steps with yields of 20-25% of the initial cell-bound 125I-labeled IgE. With phase and fluorescence microscopy, micron-size vesicles are seen which are unilamellar and spherically shaped and devoid of intracellular organelles. On dextran gradients at least 70% of the 125I-labeled IgE is bound to membranes which band at low d., indicating large, intact vesicles that are impermeable to macromols. Between 60 and 75% of the bound 125I-labeled IgE is accessible to the external medium, showing the vesicles to be predominately right side out. This prepn. was suitable for resonance energy-transfer measurements. The amphipathic, fluorescent donor and acceptor probes partition into the vesicle bilayer in a randomly distributed, noninteracting manner. The densities of the probes can be ascertained directly from the amt. of energy transfer that is obsd. as a function of acceptor concn.

L7 ANSWER 15 OF 15 CAPLUS COPYRIGHT 2003 ACS

1982:596635 Document No. 97:196635 Proteolysis of soluble IgE-receptor complexes: localization of sites on IgE which interact with the Fc receptor. Perez-Montfort, Ruy; Metzger, Henry (Arthritis Rheumatism Branch, Natl. Inst. Arthritis, Diabetes, Dig. Kidney Dis., Bethesda, MD, 20205, USA). Molecular Immunology, 19(9), 1113-25 (English) 1982. CODEN: MOIMD5. ISSN: 0161-5890.

AB Mouse and rat IgE and the resp. sol. IgE-receptor complexes purified from rat basophilic leukemia cells were digested with trypsin. The end product in each case was F(ab')2-like. It contained the C.epsilon.2 regions, had intact antigen combining sites, but had lost all ability to bind to the cell receptor for IgE. With mouse IgE, the 2 principal sites of cleavage are likely to be the interdomain regions between C.epsilon.4:C.epsilon.3 and C.epsilon.3:C.epsilon.2, resp. Cleavage at these sites occurs

sequentially with the rate const. for the cleavage at the second site being 4-fold greater than that for the initial cleavage. When IgE is bound to the receptor, the rates of cleavage are inhibited approx. 3-fold. With rat IgE, the principal initial cleavage occurs within the intrachain disulfide loop in the C.epsilon.3 domain. Even when this disulfide bond in the digested protein is reduced, the product retains a substantial binding activity. A second cleavage occurs at a similar rate as the first and at a site analogous to that seen with mouse IgE, i.e. between the C.epsilon.3 and C.epsilon.2 domains. When bound to the receptor, the rate of cleavage at the first site is inhibited 3-fold, but at the second site .gtoreq.40-fold. Thus, the C.epsilon.3 domain is the principal site of interaction between rodent IgE and its receptor.

=> s IgE vaccine
L8 12 IGE VACCINE

=> dup remove l8
PROCESSING COMPLETED FOR L8
L9 8 DUP REMOVE L8 (4 DUPLICATES REMOVED)

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L9 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2003 ACS
2002:571256 Document No. 137:168144 Long-term protective and antigen-specific effect of heat-killed Mycobacterium vaccae in a murine model of allergic pulmonary inflammation. Zuany-Amorim, Claudia; Manlius, Corinne; Trifilieff, Alexandre; Brunet, Laura R.; Rook, Graham; Bowen, Gareth; Pay, Graham; Walker, Christoph (Novartis Horsham Research Center, Novartis Pharmaceutical Ltd., Horsham, UK). Journal of Immunology, 169(3), 1492-1499 (English) 2002. CODEN: JOIMA3. ISSN: 0022-1767. Publisher: American Association of Immunologists.
AB This report examines the effect of heat-killed Mycobacterium vaccae in a mouse model of allergic pulmonary inflammation. The s.c. administration of M. vaccae 3 wk before the immunization significantly reduced Ag-induced airway hyperreactivity and the increase in the nos. of eosinophils obsd. in the bronchoalveolar lavage fluid, blood, and bone marrow, even though no detectable changes in either cytokine (IL-4, IL-13, IL-5, and IFN-.gamma.) or total IgE levels were obsd. Furthermore, transfer of splenocytes from OVA-immunized and M. vaccae-treated mice into recipient, OVA-immunized mice significantly reduced the allergen-induced eosinophilia by an IFN-.gamma.-independent mechanism, clearly indicating that the mechanism by which M. vaccae induces its inhibitory effect is not due to a redirection from a predominantly Th2 to a Th1-dominated immune response. The protective effect of M. vaccae on the allergen-induced eosinophilia lasted for at least 12 wk after its administration, and the treatment was also effective in presensitized mice. Moreover, the allergen specificity of the inhibitory effect could be demonstrated using a double-immunization protocol, where M. vaccae treatment before OVA immunization had no effect on the eosinophilic inflammation induced by later immunization and challenge with cockroach ext. Ag. Taken together, these results clearly demonstrate that M. vaccae is effective in blocking allergic inflammation by a mechanism independent of IFN-.gamma., induces long term and Ag-specific protection, and therefore has both prophylactic and therapeutic potential for the treatment of allergic diseases.

L9 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2003 ACS
2002:439831 Document No. 137:61769 Generation of therapeutic antibody responses against IgE through vaccination. Vernersson, Molly; Ledin, Anna; Johansson, Jeannette; Hellman, Lars (Department of Cell and Molecular Biology, Biomedical Center, University of Uppsala, Uppsala, S-751 24, Swed.). FASEB Journal, 16(8), 875-877, 10.1096/fj.01-0879fje (English) 2002. CODEN: FAJOEC. ISSN: 0892-6638. Publisher: Federation of American Societies for Experimental Biology.
AB IgE is the central mediator in atopic allergies such as hay fever, eczema,

and asthma; therefore, it is a prime target in the development of allergen-independent preventive treatments. We describe an active immunization strategy that has the potential to reduce IgE to a clin. significant extent. The active vaccine component is a chimeric IgE mol., C.vepsiln.2-C.vepsiln.3-C.vepsiln.4. The receptor-binding target domain, C.vepsiln.3, is derived from the recipient species, whereas the flanking domains, C.vepsiln.2 and C.vepsiln.4, are derived from an evolutionarily distant mammal. The flanking domains have dual functions, acting both as structural support for the C.vepsiln.3 domain and to break T cell tolerance by providing foreign T cell epitopes. The efficacy of the vaccine was studied in an ovalbumin-sensitized rat model. Vaccination resulted in antibody responses against IgE in all rats and in a substantial redn. in serum IgE levels in three out of four strains. The skin reactivity upon allergen challenge was significantly reduced in vaccinated animals. The vaccine appears to be safe to use as an antigen. No crosslinking activity was obsd. in sera of vaccinated animals, and the response to vaccination was reversible with time. Our results suggest that active immunization against IgE has the potential to become a therapeutic method for humans.

L9 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2003 ACS

2002:277919 Document No. 137:167729 Recombinant allergens for immunotherapy. Chapman, Martin D.; Smith, Alisa M.; Vailes, Lisa D.; Pomes, Anna (Asthma and Allergic Diseases Center, University of Virginia, Charlottesville, VA, 22903, USA). Allergy and Asthma Proceedings, 23(1), 5-8 (English) 2002. CODEN: AAPRFV. ISSN: 1088-5412. Publisher: OceanSide Publications, Inc..

AB A review. Many of the problems assocd. with using natural allergenic products for allergy diagnosis and treatment can be overcome using genetically engineered recombinant allergens. Over the past 10 yr, the most important allergens from mites, pollens, animal dander, insects, and foods have been cloned, sequenced, and expressed. Allergens have diverse biol. functions (they may be enzymes, enzyme inhibitors, lipocalins, or structural proteins). High-level expression systems have been developed to produce recombinant allergens in bacteria, yeast, or insect cells. Recombinant allergens show comparable IgE antibody binding to natural allergens and show excellent reactivity on skin testing and in in vitro diagnostic tests. Recombinant allergens will enable innovative new strategies for allergen immunotherapy to be developed. These include peptide-based vaccines, engineered hypo-allergens with reduced reactivity for IgE antibodies, nucleotide-conjugated vaccines that promote Th1 responses, and the possibility of developing prophylactic allergen vaccines.

L9 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2003 ACS

2001:635924 Document No. 135:194487 Methods of prevention and treatment of asthma and allergic conditions. Sukurkovich, Boris; Skurkovich, Simon (Advanced Biotherapy, Inc., USA). PCT Int. Appl. WO 2001062287 A1 20010830, 84 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US5660 20010223. PRIORITY: US 2000-511972 20000224.

AB The present invention relates to allergy vaccines and methods of treating and/or preventing asthma, and allergic conditions. The invention is based on the discovery that inhibiting the ligand/receptor interactions involving, e.g., IgE, IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, interferon-alpha, histamine, leukotriene, and their resp. receptors, inhibits prodn. of IgE thereby treating or preventing such diseases or conditions. Competitive inhibition of such receptor/ligand interactions is accomplished by immunizing a human or veterinary patient with the interleukin, interferon-alpha, histamine, leukotriene, their receptors, in any combination. Also, the invention relates to inhibiting receptor/ligand interactions involved in IgE prodn. by competitively inhibiting such interactions by administering antibodies to the ligands, receptors, or both, as well as by administering analogs of the receptors (e.g., sol. receptors not assocd. with a cell).

L9 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2003 ACS
2000:314492 Document No. 132:346610 Enhanced vaccines. Hellman, Lars T. (Resistentia Pharmaceuticals AB, Swed.). PCT Int. Appl. WO 2000025722 A2 20000511, 50 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-SE1896 19991021. PRIORITY: US 1998-PV106652 19981102; US 1999-401636 19990922.

AB The invention relates to methods and materials involved in the treatment and prevention of various diseases such as infections and IgE-related diseases. Specifically, the invention relates to methods and materials that can be used to vaccinate a mammal against specific self or non-self antigens. For example, the methods and materials described herein can be used to reduce the effects of IgE antibodies within a mammal by reducing the amt. of total and receptor bound IgE antibodies in the mammal. In addn., the invention provides vaccine conjugates, immunogenic polypeptides, nucleic acid mols. that encode immunogenic polypeptides, host cells contg. the nucleic acid mols. that encode immunogenic polypeptides, and methods for making vaccine conjugates and immunogenic polypeptides as well as nucleic acid mols. that encode immunogenic polypeptides. Further, the invention provides an **IgE vaccine** that induces an anti-self IgE response in a mammal.

L9 ANSWER 6 OF 8 MEDLINE DUPLICATE 1
2000069385 Document Number: 20069385. PubMed ID: 10602034. Oral anti-IgE immunization with epitope-displaying phage. Zuercher A W; Miescher S M; Vogel M; Rudolf M P; Stadler M B; Stadler B M. (Institute of Immunology, University of Bern, Inselspital, Bern, Switzerland. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (2000 Jan) 30 (1) 128-35. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB An essential requirement for oral vaccines is the ability to survive the harsh environment of the stomach in an antigenically intact form. As bacteriophages are adapted to this environment we used epitope-displaying M13 bacteriophages as carriers for an experimental oral anti-**IgE vaccine**. The feasibility of this approach was tested in a simulated gastric fluid using two different mimotopes as well as an anti-idiotypic Fab of the non-anaphylactogenic monoclonal anti-IgE antibody BSW17. All phage clones remained infective after this treatment. However, only epitopes displayed on the pVIII protein were still recognized by BSW17 whereas pIII-expressed epitopes were rapidly inactivated. Surprisingly, when used for oral immunization of mice all phage clones induced anti-IgE antibodies. In contrast, oral immunization with the purified, pVIII protein displaying the mimotope induced anti-phage but no anti-IgE antibodies. After feeding a single dose of mimotope-displaying bacteriophage, phage DNA could be detected in mouse feces for 10 days. Our results show that epitope-displaying bacteriophages can be used to induce an epitope-specific antibody response via the oral route.

L9 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2003 ACS
2000:244696 Document No. 133:57193 Immunotherapy for food allergies: past, present, future. Lehrer, Samuel B.; Wild, Laurianne G.; Bost, Kenneth L.; Sorensen, Ricardo U. (Division of Allergy and Clinical Immunology, Department of Medicine, Tulane University Medical Center, New Orleans, LA, USA). Clinical Reviews in Allergy & Immunology, 17(3), 361-381 (English) 1999. CODEN: CRAIF2. ISSN: 1080-0549. Publisher: Humana Press Inc..

AB A review with 65 refs. An overview of the gut mucosal immune response, along with the traditional and novel approaches to immunotherapy such as immune complex therapy, peptide therapy, anti-IgE and DNA immunization are

discussed. A discussion of mucosal vaccines and advances in the development of hypo-allergenic foods through biotechnol. to reduce IgE binding capacity of the allergenic proteins is also presented.

L9 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2003 ACS
1998:145086 Document No. 128:242665 Anti-IgE vaccination. Stadler, Beda M.; Vogel, Monique; Rudolf, Michael; Miescher, Sylvia; Zurcher, Adrian; Kricek, Franz (Institute of Immunology and Allergology, University of Bern, Bern, Switz.). Progress in Allergy and Clinical Immunology, Proceedings of the International Congress of Allergology and Clinical Immunology, 16th, Cancun, Mex., Oct. 19-24, 1997, 339-342. Editor(s): Oehling, Albert K.; Huerta Lopez, J. G. Hogrefe & Huber: Seattle, Wash. (English) 1997. CODEN: 65SQAB.
AB A review with 34 refs. The phage display technol. has provided a new way to dissect the natural anti-IgE response. Based on the authors' results, the question can now be addressed whether it may be possible to redirect a human anti-IgE response by active immunization with IgE-mimotopes or anti-idiotypic antibodies. To understand allergic disease, it can also be envisaged that a radical approach to eliminate or neutralize IgE will finally be the proof of how important the IgE mol. is for the pathophysiol. of the IgE mediated diseases.

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L13 ANSWER 1 OF 34 MEDLINE DUPLICATE 1
2002451888 Document Number: 22197924. PubMed ID: 12209626. Evidence for an early appearance of modern post-switch immunoglobulin isotypes in mammalian evolution (II); cloning of **IgE**, IgG1 and IgG2 from a monotreme, the duck-billed platypus, Ornithorhynchus anatinus. Vernersson M; Aveskogh M; Munday B; **Hellman Lars**. (Department of Cell and Molecular Biology, University of Uppsala, The Biomedical Center, Uppsala, Sweden. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (2002 Aug) 32 (8) 2145-55. Journal code: 1273201. ISSN: 0014-2980. Pub. country: Germany: Germany, Federal Republic of. Language: English.
AB To trace the emergence of the modern post-switch immunoglobulin (Ig) isotypes in vertebrate evolution we have studied Ig expression in mammals distantly related to eutherians. We here present an analysis of the Ig expression in an egg-laying mammal, a monotreme, the duck-billed platypus (Ornithorhynchus anatinus). Fragments of platypus IgG and **IgE** cDNA were obtained by a PCR-based screening using degenerate primers. The fragments obtained were used as probes to isolate full-length cDNA clones of three platypus post-switch isotypes, IgG1, IgG2, and **IgE**. Comparative amino acid sequence analysis against IgY, **IgE** and IgG from various animal species revealed that platypus **IgE** and IgG form branches that are clearly separated from those of their eutherian (placental) counterparts. However, the platypus **IgE** and IgG still conform to the general structure displayed by the respective Ig isotypes of eutherian and marsupial mammals. According to our findings, all of the major evolutionary changes in the expression array and basic Ig structure that have occurred since the evolutionary separation of mammals from the early reptile lineages, occurred prior to the separation of

monotremes from marsupial and placental mammals. Hence, our results indicate that the modern post-switch isotypes appeared very early in the mammalian lineage, possibly already 310-330 million years ago.

L13 ANSWER 2 OF 34 MEDLINE DUPLICATE 2
2002300838 Document Number: 22035325. PubMed ID: 11967231. Generation of therapeutic antibody responses against **IgE** through vaccination. Vernersson Molly; Ledin Anna; Johansson Jeannette; **Hellman Lars**. (Department of Cell and Molecular Biology, Biomedical Center, University of Uppsala, S-751 24 Uppsala, Sweden. ) FASEB JOURNAL, (2002 Jun) 16 (8) 875-7. Journal code: 8804484. ISSN: 1530-6860. Pub. country: United States. Language: English.

AB **IgE** is the central mediator in atopic allergies such as hay fever, eczema, and asthma; therefore, it is a prime target in the development of allergen-independent preventive treatments. We describe an active immunization strategy that has the potential to reduce **IgE** to a clinically significant extent. The active vaccine component is a chimeric **IgE** molecule, Cepsilon2-Cepsilon3-Cepsilon4. The receptor-binding target domain, Cepsilon3, is derived from the recipient species, whereas the flanking domains, Cepsilon2 and Cepsilon4, are derived from an evolutionarily distant mammal. The flanking domains have dual functions, acting both as structural support for the Cepsilon3 domain and to break T cell tolerance by providing foreign T cell epitopes. The efficacy of the vaccine was studied in an ovalbumin-sensitized rat model. Vaccination resulted in antibody responses against **IgE** in all rats and in a substantial reduction in serum **IgE** levels in three out of four strains. The skin reactivity upon allergen challenge was significantly reduced in vaccinated animals. The vaccine appears to be safe to use as an antigen. No cross-linking activity was observed in sera of vaccinated animals, and the response to vaccination was reversible with time. Our results suggest that active immunization against **IgE** has the potential to become a therapeutic method for humans.

L13 ANSWER 3 OF 34 MEDLINE DUPLICATE 3
2002699771 Document Number: 22350096. PubMed ID: 12461652. Echidna IgA supports mammalian unity and traditional Therian relationship. Belov Katherine; Zenger Kyall R; **Hellman Lars**; Cooper Desmond W. (Evolutionary Biology Unit, Australian Museum, 6 College St, Sydney, Australia 2010. ) MAMMALIAN GENOME, (2002 Nov) 13 (11) 656-63. Journal code: 9100916. ISSN: 0938-8990. Pub. country: United States. Language: English.

AB IgA is found only in birds and mammals where it is the principal immunoglobulin class found in secretions, providing protection at mucosal surfaces. The structure of IgA in birds is different from that of marsupials and eutherians. The avian heavy-chain constant region of IgA (Ca) consists of four domains, while marsupial and eutherian Ca consists of three domains plus a hinge. Here we describe the cloning and characterization of the heavy chain of IgA from the short-beaked echidna, Tachyglossus aculeatus, and report that monotreme Ca is composed of three domains plus a hinge, making it similar to its therian counterparts. The amino acid sequence identity of echidna Ca is approximately 47% with the therians and 30% with birds. Phylogenetic analysis of the Ca sequences provides strong support for the Theria hypothesis, which proposes that monotremes diverged prior to the separation of marsupial and eutherians, and directly contradicts the results of the mitochondrial data, which support a "Marsupionta" relationship which has marsupials and monotremes closer to each other. The characterization of the heavy chain of IgA from monotremes, in conjunction with the recent description of monotreme IgG and **IgE** nucleotide sequence, confirms that the "second big bang" of immunoglobulin evolution predated the divergence of extant mammals.

L13 ANSWER 4 OF 34 SCISEARCH COPYRIGHT 2003 THOMSON ISI
2002:395291 The Genuine Article (R) Number: 549CA. Generation of therapeutic antibody responses against **IgE** through vaccination. Vernersson M; Ledin A; Johansson J; **Hellman L (Reprint)**. Uppsala Univ, Ctr

Biomed, Dept Cell & Mol Biol, Box 596, S-75124 Uppsala, Sweden (Reprint); Uppsala Univ, Ctr Biomed, Dept Cell & Mol Biol, S-75124 Uppsala, Sweden; Resistentia Pharmaceut AB, S-75323 Uppsala, Sweden. FASEB JOURNAL (APR 2002) Vol. 16, No. 6, pp. U104-U124. Publisher: FEDERATION AMER SOC EXP BIOL. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA. ISSN: 0892-6638. Pub. country: Sweden. Language: English.
*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB **IgE** is the central mediator in atopic allergies such as hay fever, eczema, and asthma; therefore, it is a prime target in the development of allergen-independent preventive treatments. We describe an active immunization strategy that has the potential to reduce **IgE** to a clinically significant extent. The active vaccine component is a chimeric **IgE** molecule, Cepsilon2-Cepsilon3-Cepsilon4. The receptor-binding target domain, Cepsilon3, is derived from the recipient species, whereas the flanking domains, Cepsilon2 and Cepsilon4, are derived from an evolutionarily distant mammal. The flanking domains have dual functions, acting both as structural support for the Cepsilon3 domain and to break T cell tolerance by providing foreign T cell epitopes. The efficacy of the vaccine was studied in an ovalbumin-sensitized rat model. Vaccination resulted in antibody responses against **IgE** in all rats and in a substantial reduction in serum **IgE** levels in three out of four strains. The skin reactivity upon allergen challenge was significantly reduced in vaccinated animals. The vaccine appears to be safe to use as an antigen. No cross-linking activity was observed in sera of vaccinated animals, and the response to vaccination was reversible with time. Our results suggest that active immunization against **IgE** has the potential to become a therapeutic method for humans.

L13 ANSWER 5 OF 34 CAPLUS COPYRIGHT 2003 ACS
2000:314492 Document No. 132:346610 Enhanced vaccines. **Hellman, Lars T.** (Resistentia Pharmaceuticals AB, Swed.). PCT Int. Appl. WO 2000025722 A2 20000511, 50 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-SE1896 19991021. PRIORITY: US 1998-PV106652 19981102; US 1999-401636 19990922.

AB The invention relates to methods and materials involved in the treatment and prevention of various diseases such as infections and **IgE** -related diseases. Specifically, the invention relates to methods and materials that can be used to vaccinate a mammal against specific self or non-self antigens. For example, the methods and materials described herein can be used to reduce the effects of **IgE** antibodies within a mammal by reducing the amt. of total and receptor bound **IgE** antibodies in the mammal. In addn., the invention provides vaccine conjugates, immunogenic polypeptides, nucleic acid mols. that encode immunogenic polypeptides, host cells contg. the nucleic acid mols. that encode immunogenic polypeptides, and methods for making vaccine conjugates and immunogenic polypeptides as well as nucleic acid mols. that encode immunogenic polypeptides. Further, the invention provides an **IgE** vaccine that induces an anti-self **IgE** response in a mammal.

L13 ANSWER 6 OF 34 MEDLINE DUPLICATE 4
2001103120 Document Number: 20545223. PubMed ID: 11093157. Murine mast cell lines as indicators of early events in mast cell and basophil development. Lunderius C; Xiang Z; Nilsson G; **Hellman L.** (Department of Cell and Molecular Biology, Uppsala University, Biomedical Center, Uppsala, Sweden. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (2000 Dec) 30 (12) 3396-402. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB To study early events in mast cell / basophil development, the phenotype of a panel of murine cell lines at various stages of differentiation was determined. Based on the expression on various mast cell-specific proteases and several additional hematopoietic differentiation markers, the cell lines CFTL-15 and MCP5 / L were clearly identified as mast cells, although with a relatively immature phenotype. These two cell lines express the high-affinity **IgE** receptor alpha-chain, the mouse mast cell protease (MMCP)-5 and the carboxypeptidase A (CPA). Bone marrow-derived mast cells and the transplantable mast cell tumor MTC were shown to express the **IgE** receptor alpha-chain, MMCP-5 and CPA, as well as the mast cell tryptase MMCP-6 and the chymase MMCP-4, a protease expressed only during late stages of mast cell differentiation. These two cell types thus display a more mature mast cell phenotype. In contrast, the cell lines P815 and 32D cl3 did not express any mast cell differentiation markers. Interestingly, the IC-2 cell line was shown to express several markers for immature mast cells and in addition MMCP-8, a serine protease which may represent a marker for mouse basophils. By antibody staining, almost all IC-2 cells were shown to express MMCP-8. This indicates that individual cells may simultaneously express both mast cell and basophil markers. Moreover, these findings suggest that an early branch point in hematopoietic development where mast cells and basophils have a common precursor cell may exist.

L13 ANSWER 7 OF 34 MEDLINE DUPLICATE 5
2000452719 Document Number: 20462624. PubMed ID: 11009100. MMCP-8, the first lineage-specific differentiation marker for mouse basophils. Elevated numbers of potent IL-4-producing and MMCP-8-positive cells in spleens of malaria-infected mice. Poorafshar M; Helmby H; Troye-Blomberg M; **Hellman L.** (Department of Cell and Molecular Biology, University of Uppsala, Sweden. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (2000 Sep) 30 (9) 2660-8. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB In mice infected with the non-lethal malaria parasite Plasmodium chabaudi chabaudi AS, a prominent switch from a Th1 to a Th2 type of response occurs in CD4+ T cells at the time of peak parasitemia or shortly thereafter (9-15 days after infection). This is accompanied by a major increase in IL-4, and a similar decrease in IFN-gamma-producing cells. Non-B-non-T cells have been shown to be the main source of the IL-4 in these mice. The IL-4-producing cells are hyperresponsive to IL-3, indicating mast cell or basophil origin. To further characterize this cell population we have studied various organs at different time points of malarial infection by Northern blot analysis. No significant increase in the expression of any of the classical mouse mast cell serine proteases (MMCP)-1 to 7 or carboxypeptidase A was detected in the spleen during the entire infection. However, a marked increase in the expression of MMCP-8 was observed in the spleen at around day 15 post infection. Isolation of **IgE** receptor-positive cells from spleen shortly after peak parasitemia led to a prominent enrichment of MMCP-8-expressing cells. Fifty thousand of these cells were, after IL-3 stimulation, found to produce IL-4 to levels comparable with more than one million fully activated T cells. Our results show that basophil-like cells are very potent producers of IL-4 and that IL-4 produced by these cells may be of major importance for the initiation of a Th2 response. In addition, the detection of MMCP-8 in these cells has led to the identification of the first basophil-specific differentiation marker in the mouse.

L13 ANSWER 8 OF 34 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2000:377491 Document No.: PREV200000377491. The evolution of modern post switch isotypes; A study of immunoglobulin isotypes in marsupials and monotremes. Aveskogh, M. (1); Vernersson, M. (1); **Hellman, L. (1)** ; Munday, B.. (1) Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala Sweden. Developmental & Comparative Immunology, (2000) Vol. 24, No. Supplement 1, pp. S9. print. Meeting Info.: 8th Congress of the International Society of Developmental and Comparative Immunology Cairns, Australia July 03-06, 2000 ISSN: 0145-305X.

Language: English. Summary Language: English.

L13 ANSWER 9 OF 34 MEDLINE DUPLICATE 6
2000043989 Document Number: 20043989. PubMed ID: 10579388. Cloning and structural analysis of IgM (mu chain) and the heavy chain V region repertoire in the marsupial Monodelphis domestica. Aveskogh M; Pilstrom L; **Hellman L.** (Department of Cell and Molecular Biology, University of Uppsala, Biomedical Center, Sweden. ) DEVELOPMENTAL AND COMPARATIVE IMMUNOLOGY, (1999 Oct-Dec) 23 (7-8) 597-606. Journal code: 7708205. ISSN: 0145-305X. Pub. country: United States. Language: English.

AB To address the question of the Ig isotype repertoire of non placental mammals, we have examined the Ig expression in the marsupial Monodelphis domestica (grey short tailed opossum). Screening of an opossum spleen cDNA library has previously led to the isolation of full length clones for opossum IgG (gamma chain), **IgE** (epsilon chain) and IgA (alpha chain). We now present the isolation of several cDNA clones encoding the entire constant regions of the opossum IgM (mu chain). A comparative analysis of the amino acid sequences for IgM from various animal species showed that opossum IgM, within the various animals studied, is the most divergent member of its Ig class. However, it still conforms to the general structure of IgM in other vertebrates. Four Ig classes have now been identified in opossum and only one isotype is apparently present within each Ig class, IgM, IgG, IgA and **IgE**. Opossum has previously been shown to have a limited VH region diversity, with only two V gene families. Both of these belong to the group III of mammalian VH sequences. This limitation in variability is to some extent compensated for by a large variation in D, P and N regions, both in size and in sequence. However, evidence for the expression of only two functional J segments has so far been detected, which indicates a rather limited diversity also of the J segments in the opossum.

L13 ANSWER 10 OF 34 CAPLUS COPYRIGHT 2003 ACS
1999:56260 Document No. 130:266025 Vaccines against allergies. **Hellman, L.** (Department of Medical Immunology and Microbiology, BMC, Uppsala, S-751 23, Swed.). Handbook of Experimental Pharmacology, 133(Vaccines), 499-526 (English) 1999. CODEN: HEPHD2. ISSN: 0171-2004. Publisher: Springer-Verlag.

AB A review with 135 refs. A detailed description of allergic immune response along with a discussion of some of the currently available immunotherapies is presented. Application of modified allergens, oral administration of allergens and allergen exts., peptide vaccines, cytokine agonists and antagonists as immunotherapeutic approach is discussed. In addn., use of low mol. wt. substances that interfere with the interactions between **IgE** and its receptors as well as strategies involving the depletion of plasma and mast cell bound **IgE** by treatment with monoclonal anti-**IgE** antibodies is also mentioned. Finally, strategies involving induction of strong anti-**IgE** response by vaccination are outlined.

L13 ANSWER 11 OF 34 MEDLINE DUPLICATE 7
1998425532 Document Number: 98425532. PubMed ID: 9754561. Evidence for an early appearance of modern post-switch isotypes in mammalian evolution; cloning of **IgE**, IgG and IgA from the marsupial Monodelphis domestica. Aveskogh M; **Hellman L.** (Department of Medical Biochemistry and Microbiology, University of Uppsala, Sweden. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (1998 Sep) 28 (9) 2738-50. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB In birds, reptiles and amphibians the IgY isotype exhibits the functional characteristics of both of IgG and **IgE**. Hence, the gene for IgY most likely duplicated some time during early mammalian evolution and formed the ancestor of present day IgG and **IgE**. To address the question of when IgY duplicated and formed two functionally distinct isotypes, and to study when IgG and IgA lost their second constant domains, we have examined the Ig expression in a non-placental mammal, the

marsupial Monodelphis domestica (grey short-tailed opossum). Screening of an opossum spleen cDNA library revealed the presence of all three isotypes in marsupials. cDNA clones encoding the entire constant regions of opossum **IgE** (epsilon chain), IgG (gamma chain) and IgA (alpha chain) were isolated, and their nucleotide sequences were determined. A comparative analysis of the amino acid sequences for IgY, IgA, **IgE** and IgG from various animal species showed that opossum **IgE**, IgG and IgA on the phylogenetic tree form branches clearly separated from their eutherian counterparts. However, they still conform to the general structure found in eutherian **IgE**, IgG and IgA. Our findings indicate that all the major evolutionary changes in the Ig isotype repertoire, and in basic Ig structure that have occurred since the evolutionary separation of mammals from the early reptile lineages, occurred prior to the evolutionary separation of marsupials and placental mammals.

L13 ANSWER 12 OF 34 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2002:81032 Document No.: PREV200200081032. Vaccine comprising part of constant region of **IgE** for treatment of **IgE**-mediated allergic reactions. **Hellman, L. T.**. Vaderkvarnsgatan 11A, S-753 29 Uppsala Sweden. Patent Info.: US 5653980 Aug. 5, 1997. Official Gazette of the United States Patent and Trademark Office Patents, (Aug. 5, 1997) Vol. 1201, No. 1, pp. 362. ISSN: 0098-1133. Language: English.

L13 ANSWER 13 OF 34 MEDLINE DUPLICATE 8
1998025077 Document Number: 98025077. PubMed ID: 9321425. Cloning, structural analysis, and expression of the pig **IgE** epsilon chain. Vernersson M; Pejler G; Kristersson T; Alving K; **Hellman L** . (Department of Medical Immunology and Microbiology, University of Uppsala, Sweden. ) IMMUNOGENETICS, (1997) 46 (6) 461-8. Journal code: 0420404. ISSN: 0093-7711. Pub. country: United States. Language: English.
AB As a step in the evolutionary studies of immunoglobulin E (**IgE**) and for the purpose of developing new reagents that will facilitate a more detailed analysis of **IgE**-mediated inflammatory reactions in a large animal model, we here present the cloning of the epsilon chain of **IgE** in the domestic pig (Sus scrufa). A partial cDNA clone for the epsilon chain of pig **IgE** was isolated by polymerase chain reaction (PCR) amplification using degenerate primers directed against conserved regions in the second (CH2) and the fourth (CH4) constant domains of **IgE**. cDNA derived from mRNA isolated from the spleen and lymph nodes of a pig actively sensitized with a protein extract from the nematode Ascaris suum was used as template. Screening of a spleen cDNA library with the partial cDNA clone as probe resulted in isolation of a clone that contained the entire coding region. The nucleotide sequence was determined and was found to conform with the previously identified mammalian epsilon-chain sequences. The highest degree of similarity was found to sheep **IgE**. A DNA construct encoding a baculovirus signal sequence, a histidine hexapeptide, and the CH2-CH3-CH4 domains of the pig **IgE** epsilon chain was obtained by PCR amplification. The construct was ligated into the baculovirus expression vector pVL1392. Infection of High Five insect cells with recombinant baculovirus resulted in expression and secretion of a soluble 6 x His-CH2-CH3-CH4 protein product.

L13 ANSWER 14 OF 34 MEDLINE DUPLICATE 9
97249376 Document Number: 97249376. PubMed ID: 9095262. Is vaccination against **IgE** possible?. **Hellman L**. (Department of Medical Immunology and Microbiology, University of Uppsala. ) ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1996) 409 337-42. Ref: 18. Journal code: 0121103. ISSN: 0065-2598. Pub. country: United States. Language: English.
AB A substantial reduction in the levels of both total and antigen specific **IgE** will most likely result in improved symptom scores in atopic individuals. Based on this assumption we initiated a project to study the possibility of reducing levels of circulating and mast cell bound

**IgE**, by inducing a strong autoimmune antibody response against **IgE** in the host. Bacterially produced fusion proteins containing constant domains two (CH2) and three (CH3) of rat **IgE** directly linked to the glutathione-S-transferase (GST) protein from Schistosoma japonicum or to the maltose binding protein of Esherichia coli were used as the active components of the allergy vaccine. Injection of either of these fusion proteins together with adjuvant led to the induction of a strong autoimmune anti-**IgE** response in several **IgE** low or medium responder strains of rats. Vaccination of ovalbumin sensitised Wistar rats with the GST-C2C3 fusion protein resulted in a profound decrease in serum **IgE** levels and later in a nearly complete block in histamine release from mast cells and basophils upon challenge with either a cross-linking polyclonal anti-**IgE** antiserum or a specific allergen. This shows that it is possible to reduce **IgE** levels in an animal to such an extent that it gives a clear clinical effect. Recent studies with an extended panel of rat strains including four **IgE** high responder strains, indicate that induction of the autoimmune response is dependent on the plasma concentration of **IgE** before vaccination. A high concentration of **IgE** has a negative effect on the induction of autoimmunity, most likely by inducing a B-cell tolerance in the host. Vaccinated subjects with very high **IgE** concentrations thereby responds poorly to the vaccine. Current studies are aimed at overcoming this potential limitation of the vaccination procedure.

L13 ANSWER 15 OF 34 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 10
96297255 EMBASE Document No.: 1996297255. Allergy vaccines: A review of developments. **Hellman L.**; Carlsson M.. Department of Medical Immunology, Biomedical Centre, University of Uppsala,S-751 23 Uppsala, Sweden. Clinical Immunotherapeutics 6/2 (130-142) 1996. ISSN: 1172-7039. CODEN: CIMMEA. Pub. Country: New Zealand. Language: English. Summary Language: English.

AB Immunotherapy by vaccination (hyposensitisation) has been used since the beginning of this century for the treatment of atopic diseases. Immunotherapy is still widely used and in the hands of specialists is quite safe. However, the use of crude allergen extracts, doubts about its efficacy for many allergens and the risk of severe adverse effects when not properly administered have raised questions about the place of hyposensitisation as part of modern immunotherapy. The relatively efficient pharmacotherapy of allergic diseases has also reduced the need for traditional high dose immunotherapy. However, progress in the understanding of the basic immune mechanisms of allergy and in the characterisation of dominant allergens has stimulated the development of several novel strategies for immunotherapy. A few of these have the potential of reaching the clinic in the near future. The most promising areas of this rapidly developing field will be covered in this article. The 4 main areas which will be discussed in more detail are: (i) progress in the area of modifications :of allergen extracts or purified recombinant allergens by allergen cross-linking, monomethoxy-polyethylene glycol coupling or immune complex formation, with the aim of reducing the allergenicity of the antigen or to tolerise or redirect the immune response to a mainly T helper 1 response; (ii) oral administration of allergens or allergen extracts, possibly by using bacteria as live vaccines; (iii) treatment with immunodominant peptides from major allergens, with the aim of inducing unresponsiveness in allergen-specific T cells; and (iv) immune intervention directly targeting the **IgE** molecule, to deplete circulating and mast cell bound **IgE**, by treatment with monoclonal antibodies or by vaccination against **IgE** using parts of the **IgE** molecule covalently coupled to a foreign carrier protein.

L13 ANSWER 16 OF 34 MEDLINE DUPLICATE 11
96285637 Document Number: 96285637. PubMed ID: 8693292. Characterization of a human basophil-like cell line (LAMA-84). Blom T; Nilsson G; Sundstrom C; Nilsson K; **Hellman L.** (Department of Medical Immunology,

University of Uppsala, Sweden. ) SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (1996 Jul) 44 (1) 54-61. Journal code: 0323767. ISSN: 0300-9475. Pub. country: ENGLAND: United Kingdom. Language: English.

AB LAMA-84, a human leucocytic cell line, which upon establishment was described as having megakaryocytic, erythroid and granulocytic characteristics, was analysed for expression of various differentiation markers. In addition to some of the previously described phenotypic characteristics, this cell line was found to express mRNA for several proteins characteristic for basophilic leucocytes and mast cells. The authors show that LAMA-84 cells express mRNA for the mast cell tryptase, the proteoglycan core protein, carboxypeptidase A and the alpha and beta chains of the high affinity **IgE** receptor (Fc epsilon RI). The authors examined the potential of LAMA-84 to differentiate in serum-free medium or after DMSO or PMA treatment. Depending on the inducing factor, surface expression of the Fc epsilon RI alpha-chain was increased from 20% to 35-50% of the cells and mRNA levels for tryptase were increased in serum-free medium and after DMSO treatment. LAMA-84 was found to express CD13, CDw17, CD29, CD33, CD40, CD45 and CD117. Furthermore, mRNA for the eosinophil/basophil markers Charcot-Leyden crystal (CLC) protein and the major basic protein (MBP), as well as the erythrocyte differentiation marker alpha-globin, was detected. However, the authors observed only trace amounts of mRNA for another erythroid differentiation marker (glycophorin), trace amounts of the megakaryocytic marker GPIIIa, and no detectable level of GPIb alpha. By comparing the expression pattern of a panel of differentiation markers in LAMA-84, and a second human cell line (KU812) expressing a basophil phenotype, it is evident that these cell lines, which presently are the only two cell lines identified with basophilic characteristics, share a large number of phenotypic characteristics.

L13 ANSWER 17 OF 34 MEDLINE DUPLICATE 12

96062118 Document Number: 96062118. PubMed ID: 7481558. A single major transcript encodes the membrane-bound form of rat immunoglobulin E. Aveskogh M; **Hellman L**. (Department of Medical Immunology and Microbiology, University of Uppsala, Sweden. ) SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (1995 Nov) 42 (5) 535-9. Journal code: 0323767. ISSN: 0300-9475. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The primary structure of the membrane-bound form of rat immunoglobulin E was determined by PCR amplification and nucleotide sequence analysis of its mRNA. The sequence was found to correspond to the previously identified membrane exons of the rat epsilon chain gene. The donor splice site in the C4 exon was mapped to a position 35 nt upstream of the stop codon for the secreted form of rat **IgE**. Therefore, the membrane-bound **IgE** lacks the 12 C-terminal amino acids present in the secreted form of the protein. Recently, five novel epsilon chain transcripts were isolated from human **IgE** producing B-cells or B-cell lines. Four of these transcripts encode proteins which differ in their C-terminal ends from the classical membrane or secreted forms of human **IgE**. To investigate if these transcripts were likely to represent functional mRNAs, their evolutionary conservation was studied by screening a rat **IgE** producing B-cell line for the expression of similar transcripts. By PCR amplification and cloning of transcripts, containing both the C3 and the M2 exons, approximately 10,000 independent cDNA clones were obtained. These clones were screened with probes directed against regions specific for each of the five novel human epsilon chain mRNAs. However, no evidence was found for the presence of transcripts with a similar structure, indicating that no specific function associated with these transcripts and their corresponding proteins has been conserved between human and rat. The lack of additional M2-containing transcripts in the rat suggest that the novel human **IgE** transcripts are byproducts of differential splicing and that they most likely encode proteins with no evolutionarily important function.

L13 ANSWER 18 OF 34 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

1995:383188 Document No.: PREV199598397488. Analysis of a novel allergy vaccine designed for the treatment of **IgE**-mediated allergies. **Hellman, L.**; Carlsson, M.; Aveskogh, M.; Akerlund, R.. Dep. Med. Immunol. Microbiol., Uppsala Univ., Uppsala Sweden. 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY.. (1995) pp. 437. The 9th International Congress of Immunology. Publisher: 9th International Congress of Immunology San Francisco, California, USA. Meeting Info.: Meeting Sponsored by the American Association of Immunologists and the International Union of Immunological Societies San Francisco, California, USA July 23-29, 1995 Language: English.

L13 ANSWER 19 OF 34 MEDLINE DUPLICATE 13

94248689 Document Number: 94248689. PubMed ID: 8191224. Phenotypic characterization of the human mast-cell line HMC-1. Nilsson G; Blom T; Kusche-Gullberg M; Kjellen L; Butterfield J H; Sundstrom C; Nilsson K; **Hellman L**. (Department of Pathology, University of Uppsala, Sweden. ) SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (1994 May) 39 (5) 489-98. Journal code: 0323767. ISSN: 0300-9475. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The cell line HMC-1, derived from a patient with mast cell leukaemia, is the only established cell line exhibiting a phenotype similar to that of human mast cells. This paper reports on a detailed characterization of the expression of a panel of markers for various types of immature and mature haematopoietic cells in the HMC-1. We also studied the potential of HMC-1 to differentiate upon treatment with conditioned media from the human T-cell line Mo, retinoic acid or DMSO. HMC-1 was found to express several mast cell-related markers. A high expression of Kit, the receptor for stem-cell factor, was detected. The majority of the cells were stained with a MoAb against the mast cell-specific serine protease tryptase. Of particular interest was the finding that beta-tryptase mRNA, but not alpha-tryptase mRNA, was expressed in HMC-1. Using enzyme-histochemistry we were able to show that the beta-tryptase was enzymatically active, indicating that tryptase can form active homotetramers. Both heparin and chondroitin sulfate were found to be present in approximately equal amounts. HMC-1 lacked surface expression of the high-affinity **IgE** receptor, which was confirmed by the absence of mRNA of the alpha- and beta-chains of the **IgE** -receptor complex. However, a strong expression of the gamma-chain of the **IgE**-receptor complex was detected. A positive staining of the monocyte/macrophage marker CD68 was obtained, as well as a strong hybridization signal for the eosinophilic/basophilic-related differentiation marker the Charcot-Leyden crystal. Treatment of HMC-1 with conditioned media from the human T-cell line Mo, retinoic acid or DMSO induced only moderate changes in the surface or intracellular expression of the studied markers. The agents tested neither induced any of the monocyte/granulocyte markers examined, nor expression of the Fc epsilon RI alpha-chain.

L13 ANSWER 20 OF 34 MEDLINE DUPLICATE 14

94130960 Document Number: 94130960. PubMed ID: 8299691. Profound reduction in allergen sensitivity following treatment with a novel allergy vaccine. **Hellman L**. (Department of Immunology, University of Uppsal, Sweden. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (1994 Feb) 24 (2) 415-20. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB A novel approach is described for the treatment of **IgE**-mediated allergic reactions which is based on the induction of a strong anti- **IgE** response in the host. Vaccination of ovalbumin-sensitized rats with constant domains two and three of rat **IgE** coupled to a heterologous carrier protein resulted in a profound decrease in serum levels of **IgE**, and later in a nearly complete block of histamine release from mast cells and basophils upon challenge with either a cross-linking polyclonal anti-**IgE** antiserum or a specific allergen.

L13 ANSWER 21 OF 34 CAPLUS COPYRIGHT 2003 ACS
1993:219841 Document No. 118:219841 Vaccine comprising part of constant region of **IgE** for treatment of **IgE**-mediated allergic reactions. **Hellman, Lars T.** (Swed.). PCT Int. Appl. WO 9305810 A1 19930401, 27 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, US; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1992-SE673 19920925. PRIORITY: SE 1991-2808 19910926.

AB A vaccine for alleviating the symptoms of or preventing the induction of **IgE**-mediated allergic reactions in a mammal contains a protein having the entire amino acid sequence of the const. CH2CH3 domains of the .epsilon. chain of **IgE** mol. from the mammal species or a structurally stable subunit of said amino acid sequence contg. .gtoreq.12 amino acids, in its original or in a mutated or multimerized form, and optionally contg. an adjuvant. The cDNA sequence for CH2CH3 regions of the rat .epsilon. chain of **IgE** was cloned and ligated into a com. available vector for the prodn. of a fusion protein (purity of .apprx.50%) in Escherichia coli. Strong immune response was obtained when rats were injected s.c. with 100.mu.g of fusion protein in 0.2mL admixt. with an adjuvant.

L13 ANSWER 22 OF 34 MEDLINE DUPLICATE 15
93122085 Document Number: 93122085. PubMed ID: 8419166. Characterization of four novel epsilon chain mRNA and a comparative analysis of genes for immunoglobulin E in rodents and man. **Hellman L.** (Department of Immunology, University of Uppsala, Sweden. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (1993 Jan) 23 (1) 159-67. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB The nucleotide sequence of the 3' region of the epsilon chain gene for human **IgE** is presented. A comparison of the entire region from 5' of exon C1 to the M2 exon of the mouse, rat and human epsilon chain genes shows that the overall structure of the epsilon chain gene have changed only minimally during the 60-70 million years of evolutionary separation between rodents and man. We have previously shown that a number of rearrangements larger than 10 bp have relatively recently occurred in the C4/M1 intron of the rat or the mouse epsilon chain genes. A majority of these rearrangements were found within or in close proximity to repetitive sequences of Z-DNA-forming potential (CA dinucleotide repeats). The C4/M1 intron has evolved very rapidly, to such an extent that no apparent homology can be detected between rodents and man. Only remnants of the repetitive sequences are present in man, supporting the theory that repetitive sequences having Z-DNA-forming properties may play a role in the evolution of the eucaryote genome by promoting recombinations, leading to a rapid evolutionary drift of sequences in close proximity to these repeats. We report here the characterization of the membrane domains of human **IgE** and four novel mRNA transcribed from the human epsilon chain locus. The primary structures have been determined by polymerase chain reaction cloning and nucleotide sequence analysis. All five mRNA contain the C3 domain and the membrane exon 2 (M2). Due to frame shifts caused by novel splice sites or novel splice-site combinations, the proteins encoded by three out of these four novel mRNA differ in their carboxy-terminal end from the classical secreted or membrane-bound immunoglobulins. Northern blot analysis shows significant levels of at least three out of these four novel mRNA in an **IgE**-producing human cell line. One of the mRNA encodes a transmembrane-like structure which has characters in common with the transmembrane region of the CD3 components of the T cell receptor complex (CD3 gamma, delta and epsilon). This indicates that **IgE** -producing B cells possibly have two separate signal-transducing systems. A comparison of the classical membrane anchoring domain of the human & chain with a panel of immunoglobulin membrane domains from fish to higher mammals is presented. A tyrosine and a glutamine residue is found to be

conserved between all cytoplasmic domains of all post-switch immunoglobulin classes indicating a functional conservation of these amino acid residues.(ABSTRACT TRUNCATED AT 400 WORDS)

L13 ANSWER 23 OF 34 MEDLINE DUPLICATE 16

92347396 Document Number: 92347396. PubMed ID: 1639103. Phenotypic characterization of KU812, a cell line identified as an immature human basophilic leukocyte. Blom T; Huang R; Aveskogh M; Nilsson K; **Hellman L**. (Department of Immunology, University of Uppsala, Sweden. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (1992 Aug) 22 (8) 2025-32. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB The knowledge about the differentiation of basophilic leukocytes is fragmentary. This report discusses a detailed phenotypic characterization of molecular markers for hematopoietic differentiation in a basophilic leukemia cell line, KU812. The expression of markers for lymphoid, erythroid, neutrophil, eosinophil, monocytic, megakaryocytic, mast cell and basophil differentiation was analyzed at the mRNA level by Northern blots in the KU812 cells, and for reference, in a panel of human cell lines representative of the different hematopoietic differentiation lineages. KU812 was found to express a number of mast cell and basophil-related proteins, i.e. mast cell tryptase, mast cell carboxypeptidase A, high-affinity immunoglobulin (**IgE**) receptor alpha and gamma chains and the core protein for heparin and chondroitin sulphate synthesis. We found no expression of a number of monocyte/-macrophage or neutrophil leukocyte markers except for lysozyme. From earlier studies, it has been shown that lysozyme is not expressed in murine mucosal mast cell lines. This finding, together with the expression of the mast cell carboxypeptidase in KU812 might distinguish the phenotype of this cell line from that typical of mucosal mast cell lines in rodents. We found a low level of expression of the eosinophil and basophil marker, major basic protein, which might indicate a relationship between basophils and eosinophils. No expression is, however, detected with the eosinophil-specific markers eosinophil cationic protein, eosinophil-derived neurotoxin or eosinophil peroxidase. We also report an extensive screening for inducers of basophilic differentiation of the KU812 cells. The most efficient protocol of induction included serum starvation which led to a dramatic increase in a number of markers specific for mast cells and basophils such as tryptase, carboxypeptidase A and the heparin core protein. Finally, diisopropylfluorophosphate analysis of total protein extracts from KU812 show four labeled protein bands with sodium dodecyl sulfate-polyacrylamide gel electrophoresis, indicating that this cell line expresses at least three previously undescribed serine proteases of which one or more could be a potential basophil-specific marker(s).

L13 ANSWER 24 OF 34 MEDLINE DUPLICATE 17

92086826 Document Number: 92086826. PubMed ID: 1749921. Enhancement of **IgE** synthesis in the human myeloma cell line U-266 with an **IgE** binding factor from a human T-cell line. Nilsson G; Jernberg H; **Hellman L**; Ahlstedt S; Nilsson K. (Department of Immunology, Uppsala University, Sweden. ) SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (1991 Dec) 34 (6) 721-6. Journal code: 0323767. ISSN: 0300-9475. Pub. country: ENGLAND: United Kingdom. Language: English.

AB An **IgE**-binding factor(s) (**IgE**-BF(s] was partially purified from the supernatant of human HTLV-II carrying T-cell line MO. This **IgE**-BF(s) was shown to increase the **IgE** synthesis in the human myeloma cell line U-266, but did not affect its viability or growth. The effect of the **IgE**-BF(s) was dose-dependent and selective for **IgE** protein synthesis as beta 2-microglobulin synthesis in the U-266 and the immunoglobulin production in the U-1958 IgG-secreting human myeloma cell line were unaffected. The **IgE** -BF(s) increased the production of the epsilon heavy chain but not the lambda light chain production. The **IgE**-BF(s) was distinct from IL-1 beta, IL-3, IL-4, IL-5, IL-6, TNF-alpha, IFN-alpha, -beta, -gamma,

M-CSF, and fragments of CD23.

L13 ANSWER 25 OF 34 SCISEARCH COPYRIGHT 2003 THOMSON ISI
91:663258 The Genuine Article (R) Number: GT222. ENHANCEMENT OF **IGE** SYNTHESIS IN THE HUMAN MYELOMA CELL-LINE U-266 WITH AN **IGE** BINDING-FACTOR FROM A HUMAN T-CELL LINE. NILSSON G (Reprint); JERNBERG H; **HELLMAN L**; AHLSTEDT S; NILSSON K. UNIV HOSP UPPSALA, DEPT PATHOL, TUMOR BIOL LAB, UPPSALA, SWEDEN; PHARMACIA DIAGNOST AB, UPPSALA, SWEDEN; UNIV UPPSALA, DEPT IMMUNOL, S-75105 UPPSALA, SWEDEN. SCANDINAVIAN JOURNAL OF IMMUNOLOGY (1991) Vol. 34, No. 6, pp. 721-726. Pub. country: SWEDEN. Language: ENGLISH.
*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB An **IgE**-binding factor(s) (**IgE**-BF(s)) was partially purified from the supernatant of human HTLV-II carrying T-cell line MO. This **IgE**-BF(s) was shown to increase the **IgE** synthesis in the human myeloma cell line U-266, but did not affect its viability or growth. The effect of the **IgE**-BF(s) was dose-dependent and selective for **IgE** protein synthesis as beta-2-microglobulin synthesis in the U-266 and the immunoglobulin production in the U-1958 IgG-secreting human myeloma cell line were unaffected. The **IgE** -BF(s) increased the production of the epsilon-heavy chain but not the lambda-light chain production. The **IgE**-BF(s) was distinct from IL-1-beta, IL-3, IL-4, IL-5, IL-6, TNF-alpha, IFN-alpha, -beta, -gamma, M-CSF, and fragments of CD23.

L13 ANSWER 26 OF 34 MEDLINE DUPLICATE 18
88255082 Document Number: 88255082. PubMed ID: 3133230. Immunoglobulin synthesis in the human myeloma cell line U-266; expression of two immunoglobulin heavy chain isotypes (epsilon and alpha) after long-term cultivation in vitro. **Hellman L**; Josephson S; Jernberg H; Nilsson K; Pettersson U. (Department of Medical Genetics and Microbiology, Biomedical Center, Uppsala, Sweden. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (1988 Jun) 18 (6) 905-10. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.
AB A human **IgE**-producing myeloma has been cultivated in vitro as a continuous cell line (U-266) since 1968. Analysis of immunoglobulin production during early passages of the cell line demonstrated a high synthesis rate of monoclonal **IgE**. Analysis of late passages, cultivated after 1980, revealed a 3-6-fold lower rate of **IgE** secretion. This decrease was accompanied by the appearance of small amounts of IgA in the culture medium together with **IgE**. RNA was extracted from a late passage of U-266 and analyzed by Northern blotting, using epsilon and alpha-specific oligonucleotides as hybridization probes. The results showed the presence of epsilon as well as alpha-specific mRNA. Moreover the results demonstrated that the latter mRNA was derived from the alpha 2 locus and that the epsilon and the alpha 2-specific mRNA contained the same V region sequences. Southern blot analysis of DNA from the late passage of the U-266 cell line failed to reveal a recombinatory switch from the epsilon locus to the alpha 2 locus. The expression of alpha 2 is thus likely to be caused by differential splicing rather than by an isotype switch at the DNA level.

L13 ANSWER 27 OF 34 CAPLUS COPYRIGHT 2003 ACS
1988:584687 Document No. 109:184687 A rapidly evolving region in the immunoglobulin heavy chain loci of rat and mouse: postulated role of (dC-dA)n.cntdot.(dG-dT)n sequences. **Hellman, Lars**; Steen, Marie Louise; Sundvall, Mats; Pettersson, Ulf (Biomed. Cent., Univ. Uppsala, Uppsala, S-751 23, Swed.). Gene, 68(1), 93-100 (English) 1988. CODEN: GENED6. ISSN: 0378-1119.
AB The nucleotide sequences of the introns that are located between the C4 exon and the first membrane exon of mouse and rat Ig .epsilon.-chain genes were detd. The rat intron sequence contains 4 sep. clusters of repetitive sequences, all of which consisted of (dC-dA)n.cntdot.(dG-dT)n dinucleotide repeats. A comparison between this chromosomal region in mouse and rat revealed 4 deletions or duplications, three of which have occurred inside

or at the borders of the CA clusters. Rearrangements have occurred inside or at the borders of all 4 repeats after the evolutionary sepn. of mouse and rat. The sequence comparisons reveals in addn. a duplication, connected to the CA repeats, which has occurred early in evolution, before the evolutionary divergence of mouse and rat. These findings suggest that (dC-dA)n.cntdot.(dG-dT)n sequences are potential targets for recombination events.

L13 ANSWER 28 OF 34 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 19

1988:123473 Document No.: BR34:59335. CHARACTERIZATION OF THE RECEPTOR BINDING PART OF RAT **IGE** TO RBL CELLS BY CONSTRUCTION OF CHIMERIC ANTIBODIES. STEEN M-L; **HELLMAN L**; PETTERSSON U. DEP. MED. GENET., UPPS. UNIV., BOX 589, UPPSALA, SWED.. EIGHTEENTH ANNUAL GENERAL MEETING OF THE SCANDINAVIAN SOCIETY FOR IMMUNOLOGY, UPPSALA, SWEDEN, JUNE 2-4, 1987. SCAND J IMMUNOL. (1987) 26 (3), 330. CODEN: SJIMAX. ISSN: 0300-9475. Language: English.

L13 ANSWER 29 OF 34 SCISEARCH COPYRIGHT 2003 THOMSON ISI

85:640019 The Genuine Article (R) Number: AUD52. IMMUNOGLOBULIN-E - STRUCTURES AND EXPRESSION - STUDIES ON 3 SPONTANEOUS **IGE** -PRODUCING MYELOMAS. **HELLMAN L (Reprint)**; STEEN M L; PETTERSSON U; ENGSTROM A; KARLSSON J; BENNICH H; JERNBERG H; NILSSON K. UNIV UPPSALA, DEPT MED GENET, S-75105 UPPSALA, SWEDEN; UNIV UPPSALA, DEPT IMMUNOL, S-75105 UPPSALA, SWEDEN; UNIV UPPSALA, DEPT PATHOL, S-75105 UPPSALA, SWEDEN. SCANDINAVIAN JOURNAL OF IMMUNOLOGY (1985) Vol. 22, No. 4, pp. 445. Pub. country: SWEDEN. Language: ENGLISH.

L13 ANSWER 30 OF 34 MEDLINE DUPLICATE 20

86137407 Document Number: 86137407. PubMed ID: 3005118. Nonfunctional immunoglobulin light chain transcripts in two **IgE**-producing rat immunocytomas; implications for the allelic exclusion and transcription activation processes. **Hellman L**; Steen M L; Pettersson U. GENE, (1985) 40 (1) 115-24. Journal code: 7706761. ISSN: 0378-1119. Pub. country: Netherlands. Language: English.

AB The rearrangement and expression of immunoglobulin light-chain genes have been studied in two **IgE**-producing immunocytomas, IR2 and IR162. In the IR2 tumor only one of the kappa-chain alleles is rearranged, expressing a full-length kappa-chain polypeptide. In IR162 one of the kappa-chain alleles is functionally rearranged, expressing a 1200-nucleotide (nt) long mRNA, which encodes a functional 23-kDal kappa-chain polypeptide. The second kappa-chain allele is aberrantly rearranged; i.e., a different V region is connected to a position that is located between the J cluster and the C kappa exon. Two mRNAs which are 750 and 850 nt are transcribed from the aberrantly rearranged allele, both of which appear to encode a 12-kDal polypeptide consisting of a signal sequence that is connected directly to the C region. The levels of expression from the two kappa-chain alleles are approximately the same, suggesting that no specific mechanism exists to suppress expression of a nonfunctional allele. The rat genome contains a single lambda-chain locus which includes two C-region exons. Although this locus remains in the germ-line configuration in the IR2 and the IR162 tumors, transcripts from the C lambda I and C lambda II regions were detected at a low level in both tumors. These transcripts were detected in RNA from the immunocytomas but not in rat liver RNA indicating that expression is tissue-specific. They lacked V-region sequences and resemble so-called sterile transcripts which are expressed at a low level from unrearranged mu- and kappa-chain genes.

L13 ANSWER 31 OF 34 MEDLINE DUPLICATE 21

86137406 Document Number: 86137406. PubMed ID: 3005117. Structure and expression of kappa-chain genes in two **IgE**-producing rat immunocytomas. **Hellman L**; Engstrom A; Bennich H; Pettersson U. GENE, (1985) 40 (1) 107-14. Journal code: 7706761. ISSN: 0378-1119. Pub. country: Netherlands. Language: English.

AB The light chain expression in two **IgE**-producing rat immunocytomas, IR2 and IR162, was studied. Both immunocytomas produce light chains of the kappa type. The kappa chains were characterized at the protein level by sodium dodecylsulfate (SDS)-polyacrylamide gel electrophoresis (PAGE) and amino acid (aa) sequencing. cDNA clones corresponding to the kappa-chain mRNA were also prepared and sequenced. The results showed that rat kappa chains have the same structure as their mouse counterparts with respect to signal sequence cleavage, somatic mutations in the V-J region and invariance of all the aa positions which are strongly conserved in the frame work regions of mouse V kappa chains (greater than 95% conservation). Results from studies on kappa-chain transcription lend support to the allelic exclusion model with only one functionally expressed light chain in each immunocytoma.

L13 ANSWER 32 OF 34 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 22

1985:232760 Document No.: BA79:12756. RAT IMMUNOGLOBULIN E HEAVY CHAIN LOCUS. STEEN M-L; **HELLMAN L**; PETTERSSON U. DEPARTMENT MEDICAL GENETICS MICROBIOLOGY, UPPSALA UNIVERSITY, BIOMEDICAL CENTRE, BOX 589, S-751 23 UPPSALA, SWEDEN.. J MOL BIOL, (1984) 177 (1), 19-32. CODEN: JMOBAK. ISSN: 0022-2836. Language: English.

AB A 2100 base-pair long sequence was established which covers all 4 constant domains of the rat .epsilon.-chain. An analysis of mRNA from an **IgE** producing rat immunocytoma revealed 2 separate .epsilon.-chain mRNA species, 2.3 .times. 103 and 2.8 .times. 103 base-pairs long. The latter mRNA encodes the membrane binding form of the .epsilon.-chain. The membrane exons which are located .apprx. 2 .times. 103 base-pairs away from the 3'-side of the CH4 exon were also sequenced. A comparison between the rat and mouse .epsilon.-chains at the protein sequence level revealed an overall homology of 80% which, as expected, is considerably higher than the homology found between rat and human .epsilon.-chains. The 4th constant domain together with the 2 membrane exons exhibited the highest degree of homology, 81-89%. Only 2 differences were found when the .epsilon.-chains from LOU and Sprague Dawley rats were compared. The most striking difference at the nucleotide sequence level between the rat, mouse and human .epsilon. genes was found within the 1st intron. The mouse genome contains a unique 366 base-pair long sequence in this region. The inserted sequence is repetitive and present in .apprx. 100 copies in the mouse genome. It is flanked by 22 base-pair long direct repeats and contains also 14 base-pair long inverted repeats, thus having properties in common with transposable elements.

L13 ANSWER 33 OF 34 CAPLUS COPYRIGHT 2003 ACS

1983:28841 Document No. 98:28841 Structure and evolution of the heavy chain from rat immunoglobulin E. **Hellman, Lars**; Pettersson, Ulf; Engstroem, Aake; Karlsson, Torbjoern; Bennich, Hans (Dep. Med. Genet., Biomed. Cent., Uppsala, S-75123, Swed.). Nucleic Acids Research, 10(19), 6041-9 (English) 1982. CODEN: NARHAD. ISSN: 0305-1048.

AB The nucleotide sequence of the rat .epsilon.-chain mRNA was detd. by sequencing cloned cDNA copies of the mRNA. The established sequence covers the coding region, the 3'-noncoding region, and most of the 5'-noncoding region. A comparison with the nucleotide sequence of the human .epsilon.-chain const. region reveals that C3 and C4 are the most highly conserved domains. The rat .epsilon.-chain contains a C-terminal decapeptide which is not present in the human counterpart.

L13 ANSWER 34 OF 34 MEDLINE DUPLICATE 23

82174576 Document Number: 82174576. PubMed ID: 6803238. Characterization and molecular cloning of the mRNA for the heavy (epsilon) chain of rat immunoglobulin E. **Hellman L**; Pettersson U; Bennich H. PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1982 Feb) 79 (4) 1264-8. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB We report a study of the mRNA for the heavy (epsilon) chain of rat **IgE**. Cytoplasmic RNA was prepared from the two rat immunocytomas

IR2 and IR162 and fractionated by sucrose gradient centrifugation. An enriched fraction containing approximately 5% mRNA for the epsilon chain was obtained in this way. When translated in vitro, it produced a 59,000-dalton polypeptide, which in the presence of a membrane fraction yielded a 90,000-dalton polypeptide, presumably through posttranslational modification. Both polypeptides were precipitated by rabbit antisera that were monospecific for rat epsilon chains. The epsilon chain mRNA was estimated to be approximately 2200 nucleotides long and constitutes a minute fraction in the total mRNA both in the IR2 and the IR162 tumors, unlike the mRNA for light chains. Double-stranded cDNA copies prepared frm the RNA fraction, which was enriched for epsilon chain mRNA, were inserted into the Pst I cleavage site of the pBR322 vector. Twenty clones with inserts exceeding 1000 base pairs were used for selection of mRNA from the IR2 tumor. By in vitro translation of the selected mRNA, one clone was identified that yielded a polypeptide with the same size as the unprocessed epsilon chain. The nucleotide sequence was determined for part of the inserted cDNA in this candidate clone and was found to be homologous to a sequence in the constant region (C) of the human epsilon chain. In this communication we report a sequence from the C epsilon 3 domain of the rat **IgE**. When compared to the corresponding sequence of human **IgE**, 55% of the amino acids in the rat sequence were found to be conserved.

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| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 150.62 | 150.83 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -20.83 | -20.83 |

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L14 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS
TI Enhanced vaccines
IN Hellman, Lars T.
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
AB The invention relates to methods and materials involved in the treatment and prevention of various diseases such as infections and IgE-related diseases. Specifically, the invention relates to methods and materials that can be used to vaccinate a mammal against specific self or non-self antigens. For example, the methods and materials described herein can be used to reduce the effects of IgE antibodies within a mammal by reducing the amt. of total and receptor bound IgE antibodies in the mammal. In addn., the invention provides **vaccine conjugates**, **immunogenic polypeptides**, nucleic acid mols. that encode **immunogenic polypeptides**, host cells contg. the nucleic acid mols. that encode **immunogenic polypeptides**, and methods for making **vaccine conjugates** and **immunogenic polypeptides** as well as nucleic acid mols. that encode **immunogenic polypeptides**. Further, the invention provides an IgE **vaccine** that induces an anti-**self IgE** response in a mammal.

=> d his

(FILE 'HOME' ENTERED AT 15:57:49 ON 21 NOV 2001)

FILE 'EMBASE, BIOSIS, MEDLINE, CAPLUS' ENTERED AT 15:58:03 ON 21 NOV 2001
L1 87735 S IGE
L2 2303 S IMMUNOGENIC? (P) POLYPEPTIDE?
L3 3096531 S POLYPEPTIDE? OR CONJUGATE? OR COMPLEX?
L4 29179 S L3 (P) (IMMUNOGENIC? OR VACCINE?)
L5 303 S L4 (P) L1
L6 0 S L5 (P) ((OPOSSUM OR PLATYPUS OR KOALA OR KANGAROO OR WALLABY
L7 0 S L5 (P) MAMMAL? (P) (NON-PLACENTAL (W) MAMMAL)
L8 0 S L5 (P)(CH2) (W) (CH3) (P) (CH4)
L9 0 S L5 (P) POLYCLONAL?
L10 2 S L5 AND POLYCLONAL?
L11 18 S SELF-IGE
L12 1 S NON (W) SELF (W) IGE
L13 18 S SELF (W) IGE
L14 1 S L4 AND L13

=>

09/401,636

~~09/605,129~~

L10 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2001 ACS
TI Peptide composition as immunogen for the treatment of allergy
IN Wang, Chang Yi; Walfield, Alan M.
SO PCT Int. Appl., 155 pp.
CODEN: PIXXD2
AB The invention provides peptides comprising a sequence homologous to a portion of the third const. domain of the epsilon heavy chain of IgE, covalently linked to either (1) a carrier protein, or (2) a helper T cell epitope, and optionally to other immunostimulatory sequences as well. The invention provides for the use of such peptides as immunogens to elicit the prodn. in mammals of high titer **polyclonal** antibodies, which are specific to a target effector site on the epsilon heavy chain of IgE. The peptides are expected to be useful in pharmaceutical compns., to provide an immunotherapy for IgE-mediated allergic diseases.

L10 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
TI Monoclonal antibodies to CD40 ligand, pharmaceutical composition comprising the same and hybridomas producing the same
IN Armitage, Richard J.; Fanslow, William C.; Spriggs, Melanie K.
SO U.S., 59 pp., Cont.-in-part of U.S. Ser. No. 969,703, abandoned.
CODEN: USXXAM
AB Disclosed is a **polypeptide** (CD40-L) and DNA sequences, vectors and transformed host cells useful in providing CD40-L **polypeptides**. More particularly, this invention provides isolated human and murine CD40-L **polypeptides** that bind to the extracellular binding region of a CD40 receptor. The invention further provides CD40-L fragment for prodn. of monoclonal antibodies specific for CD40-L. Also, sol. CD40 protein and CD40 fusion proteins are prepd. for inducing B cell proliferation and antibody (e..g **IgE**) secretion, and for anti-allergic treatment. Also, fusion proteins comprising sol. human or murine CD40-L and Fc or trimeric CD40-L are constructed. In summary, CD40 agonists (i.e. membrane-bound CD40-L and oligomeric CD40-L) are provided for use as **vaccine** adjuvant and antibody prodn. stimulant, and CD40 antagonists (i.e. CD40 receptor, CD40/Fc, and sol. monomeric CD40-L) are provided for treating autoimmune diseases.

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| NEWS | 5 | Feb 19 | Access via Tymnet and SprintNet Eliminated Effective 3/31/02 |
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FILE 'HOME' ENTERED AT 11:08:09 ON 17 JUN 2002

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=>  file medline embase biosis scisearch caplus
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'MEDLINE' ENTERED AT 11:08:20 ON 17 JUN 2002

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=> s IgE fusion protein
L1            2 IGE FUSION PROTEIN

=> dup remove l1
PROCESSING COMPLETED FOR L1
L2            2 DUP REMOVE L1 (0 DUPLICATES REMOVED)

=> d l2 1-2 cbib abs

L2   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2002 ACS
2001:50815  Document No. 134:130249  Fc.epsilon. receptor fusions with chemi-
     or bioluminescence-inducing proteins and their uses in IgE detection.
     Weber, Eric R.; Wood, Keith V.; Hall, Mary P. (Heska Corporation, USA;
     Promega Corporation).  PCT Int. Appl. WO 2001004310 A1 20010118, 104 pp.
     DESIGNATED STATES: W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ,
     CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
     HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
     LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG,
     SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY,
     KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE,
     DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN,
     TD, TG.  (English).  CODEN: PIXXD2.  APPLICATION: WO 2000-US19070
     20000713.  PRIORITY: US 1999-PV143612 19990713; US 2000-PV186412 20000302.
AB   The present invention relates to chimeric genes for Fc.epsilon. receptor
     fused to bioluminescence- or chemiluminescence-inducing proteins, fusion
     proteins encoded by such nucleic acid mols., and methods of using such
     proteins and nucleic acid mols. for the detection of IgE and for
     identifying compds. capable of inhibiting Fc.epsilon. receptor activity.
     Thus, chimeric genes encoding human Fc.epsilon. receptor extracellular
     domain fused to luciferase or alk. phosphatase were constructed and
     expressed in Escherichia coli.  These fusion proteins were used in
     detection of anti-flea saliva antigen or anti-Dermatophagoides
     pteronyssinus antigen IgE in allergy patients' sera.

L2   ANSWER 2 OF 2  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1994:46608  Document No.: PREV199497059608. High level expression and
     characterization of a recombinant CD4-IgE-fusion
     protein. Kufer, P.; Krauss, S.; Person, S.; Federle, C.; Rieber,
     E. P.; Riethmueller, G.. Inst. Immunol., Muenchen Germany. Immunobiology,
     (1993) Vol. 189, No. 1-2, pp. 228. Meeting Info.: 24th Meeting of the
     Society for Immunology Leipzig, Germany September 30-October 2, 1993 ISSN:
```

0171-2985. Language: English.

=> s IgE
L3 108337 IGE

=> s l3 and CH3 domain
L4 44 L3 AND CH3 DOMAIN

=> s k4 and CH2 and CH4 domain
L5 0 K4 AND CH2 AND CH4 DOMAIN

=> s l4 and self
L6 1 L4 AND SELF

=> d l6 cbib abs

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
2002:210523 Document No. 136:323700 A minimal receptor-Ig chimera of human Fc.epsilon.RI .alpha.-chain efficiently binds secretory and membrane **IgE**. Vangelista, Luca; Cesco-Gaspere, Michela; Lorenzi, Roberto; Burrone, Oscar (Molecular Immunology, International Centre for Genetic Engineering and Biotechnology, Trieste, 34012, Italy). Protein Engineering, 15(1), 51-57 (English) 2002. CODEN: PRENE9. ISSN: 0269-2139. Publisher: Oxford University Press.
AB The authors constructed a sol. minimal receptor-Ig chimera in which the two extracellular domains of human Fc.epsilon.RI .alpha.-chain (D1 and D2) were fused to the dimerizing C-terminal domain of human IgG1 heavy chain (.gamma.1-CH3). The protein was expressed and actively secreted by Chinese hamster ovary (CHO) cells as a fully glycosylated sol. dimeric protein. It showed efficient binding both to human membrane-bound **IgE** isoforms and to the two secretory **IgE** isoforms. Moreover, the dimeric receptor binds **IgE** with the expected 1:2 stoichiometry. The receptor-Ig chimera, in 2-fold molar excess, inhibited engagement of secretory **IgE** to rat basophilic leukemia cells expressing the human .alpha..beta..gamma. receptor. Full **self** -nature and inability to bind Fc.gamma. receptors make this protein an attractive candidate for clin. applications and a novel biotechnol. tool for atopic allergy research.

=> d his

(FILE 'HOME' ENTERED AT 11:08:09 ON 17 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 11:08:20 ON 17 JUN 2002
L1 2 S IGE FUSION PROTEIN
L2 2 DUP REMOVE L1 (0 DUPLICATES REMOVED)
L3 108337 S IGE
L4 44 S L3 AND CH3 DOMAIN
L5 0 S K4 AND CH2 AND CH4 DOMAIN
L6 1 S L4 AND SELF

=> dup remove l4
PROCESSING COMPLETED FOR L4
L7 20 DUP REMOVE L4 (24 DUPLICATES REMOVED)

=> s l7 and rat
L8 1 L7 AND RAT

=> d l8 cbib abs

L8 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
2002:210523 Document No. 136:323700 A minimal receptor-Ig chimera of human Fc.epsilon.RI .alpha.-chain efficiently binds secretory and membrane **IgE**. Vangelista, Luca; Cesco-Gaspere, Michela; Lorenzi, Roberto; Burrone, Oscar (Molecular Immunology, International Centre for Genetic Engineering and Biotechnology, Trieste, 34012, Italy). Protein Engineering, 15(1), 51-57 (English) 2002. CODEN: PRENE9. ISSN: 0269-2139. Publisher: Oxford University Press.
AB The authors constructed a sol. minimal receptor-Ig chimera in which the two extracellular domains of human Fc.epsilon.RI .alpha.-chain (D1 and D2) were fused to the dimerizing C-terminal domain of human IgG1 heavy chain (.gamma.1-CH3). The protein was expressed and actively secreted by Chinese hamster ovary (CHO) cells as a fully glycosylated sol. dimeric protein. It showed efficient binding both to human membrane-bound **IgE** isoforms and to the two secretory **IgE** isoforms. Moreover, the dimeric receptor binds **IgE** with the expected 1:2 stoichiometry. The receptor-Ig chimera, in 2-fold molar excess, inhibited engagement of secretory **IgE** to **rat** basophilic leukemia cells expressing the human .alpha..beta..gamma. receptor. Full self-nature and inability to bind Fc.gamma. receptors make this protein an attractive candidate for clin. applications and a novel biotechnol. tool for atopic allergy research.

=> s rat IgE
L9 1010 RAT IGE

=> s l9 and CH3 domain
L10 0 L9 AND CH3 DOMAIN

=> d his

(FILE 'HOME' ENTERED AT 11:08:09 ON 17 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 11:08:20 ON 17 JUN 2002
L1 2 S IGE FUSION PROTEIN
L2 2 DUP REMOVE L1 (0 DUPLICATES REMOVED)
L3 108337 S IGE
L4 44 S L3 AND CH3 DOMAIN
L5 0 S K4 AND CH2 AND CH4 DOMAIN
L6 1 S L4 AND SELF
L7 20 DUP REMOVE L4 (24 DUPLICATES REMOVED)
L8 1 S L7 AND RAT
L9 1010 S RAT IGE
L10 0 S L9 AND CH3 DOMAIN

=> s l4 and CH2 domain
L11 7 L4 AND CH2 DOMAIN

=> dup remove l11
PROCESSING COMPLETED FOR L11
L12 3 DUP REMOVE L11 (4 DUPLICATES REMOVED)

=> d l12 1-3 cbib abs

L12 ANSWER 1 OF 3 MEDLINE DUPLICATE 1
2002114858 Document Number: 21838713. PubMed ID: 11849310. IgG4 breaking the rules. Aalberse Rob C; Schuurman Janine. (Department of Immunopathology, CLB, Amsterdam, The Netherlands.. aalberse@clb.nl) . IMMUNOLOGY, (2002 Jan) 105 (1) 9-19. Ref: 66. Journal code: 0374672. ISSN: 0019-2805. Pub. country: England: United Kingdom. Language: English.
AB Immunoglobulin G4 (IgG4) antibodies have been known for some time to be

functionally monovalent. Recently, the structural basis for this monovalency has been elucidated: the in vivo exchange of IgG half-molecules (one H-plus one L-chain) among IgG4. This process results in bispecific antibodies that in most situations will behave as functionally monovalent antibodies. The structural basis for the abnormal behaviour of IgG4 seems to be largely the result of a single amino acid change relative to human IgG1: the change of a proline in core hinge of IgG1 to serine. This results in a marked shift in the equilibrium between interchain disulphide bridges and intrachain disulphide bridges, which for IgG4 results in 25-75% absence of a covalent interaction between the H-chains. Because of strong non-covalent interactions between the **CH3 domains** (and possibly also between the CH1 domain and the trans-**CH2 domain**) IgG4 is a stable four-chain molecule and does not easily exchange half-molecules under standard physiological conditions in vitro. We postulate that the exchange is catalysed in vivo by protein disulphide isomerase (PDI) and/or FcRn (the major histocompatibility complex (MHC)-related Fc receptor) during transit of IgG4 in the endosomal pathway in endothelial cells. Because IgG4 is predominantly expressed under conditions of chronic antigen exposure, the biological relevance of this exchange of half-molecules is that it generates antibodies that are unable to form large immune complexes and therefore have a low potential for inducing immune inflammation. In contrast to monovalent immunoglobulin fragments, these scrambled immunoglobulins have a normal half-life. The significance of the ensuing bispecificity needs further evaluation, because this will be relevant only in situations where high IgG4 responses are found to two unrelated antigens that happen to be present in the body at the same time and place. In this context the significance of IgG4 autoreactivity might have to be re-evaluated. The main function of IgG4, however, is presumably to interfere with immune inflammation induced by complement-fixing antibodies, or, in the case of helminth infection or allergy, by **IgE** antibodies.

L12 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS

1994:75110 Document No. 120:75110 Epitope mapping of the site(s) of binding of Fc.epsilon.RII/CD23 within human **IgE**. Determination of the B lymphocyte-binding sites by use of synthetic peptides and anti-peptide antibodies representative of linear Fc sequences. Ghaderi, Abbas A.; Stanworth, Denis R. (Dep. Microbiol. Immunol., Shiraz Univ. Med. Sci., Shiraz, Iran). Mol. Immunol., 30(18), 1655-63 (English) 1993. CODEN: MOIMD5. ISSN: 0161-5890.

AB The work undertaken has investigated the structure-function relation between **IgE** and its low affinity receptor on B lymphocytes. To identify sites on the **IgE** mols. which interact with the low affinity receptor (Fc.epsilon.RII/CD23), 10 different peptide sequences within the CH2, CH3 and CH4 domains of human **IgE** were selected according to charge, overall hydrophobicity and possible accessibility on native **IgE** sequences. Peptides representative of these were synthesized by the solid phase procedure; and their cytophilic activities were examd. by detg. their capacity to inhibit the binding of radiolabeled or erythrocyte-bound **IgE** to a Fc.epsilon.RII/CD23 pos. B cell line (RPMI-8866). Moreover, these linear sequences were rendered immunogenic by conjugation to a protein carrier (KLH) and used to produce polyclonal antibodies in rabbits. The reactivity of the anti-peptide antibodies with both free peptides and native **IgE** bound to a solid phase, as well as their capacity to inhibit binding of **IgE** to a Fc.epsilon.RII/CD23 pos. cell line, were investigated. Results from such use of peptides and anti-peptide antibodies indicate that two sequences, representative of residues 364-383 and 401-415, could be involved in the binding of **IgE** to both membrane-bound and sol. form Fc.epsilon.RII/CD23; indicating that the B lymphocyte-binding site on human **IgE** may be restricted to the **CH3 domain**

L12 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2002 ACS
1986:146780 Document No. 104:146780 Localization of epitopes of IgG Fc responsible for antibody-dependent cell-mediated cytotoxicity. Gergely, J.; Sarmay, J. (Sect. Immunol., Univ. Lajos Eotvos, Budapest, Hung.). Immunologiya (Moscow) (5), 27-30 (Russian) 1985. CODEN: IMUNDA. ISSN: 0206-4952.
AB Ig Fc-receptors (FcR) of human lymphocytes are of two types: monomeric receptors (FcR-I) having a mol. wt. of 60,000 daltons, and polymeric, membrane-fixed receptors (FcR-II). By studying the inhibitory effects of various synthetic peptides (corresponding to parts of the CH2- and **CH3-domains** of IgG and part of the CH4-domain of **IgE**) on antibody-dependent cell-mediated cytotoxicity, it was concluded that sequences interacting with one of the FcR-II binding sites are located in the **CH2-domain** Lys274-Arg301 and in the **CH3-domain** Ser408-Arg416.

=> d his

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 11:08:20 ON 17 JUN 2002

| | | |
|---|---|---|
| L1 | 2 | S IGE FUSION PROTEIN |
| L2 | 2 | DUP REMOVE L1 (0 DUPLICATES REMOVED) |
| L3 | 108337 | S IGE |
| L4 | 44 | S L3 AND CH3 DOMAIN |
| L5 | 0 | S K4 AND CH2 AND CH4 DOMAIN |
| L6 | 1 | S L4 AND SELF |
| L7 | 20 | DUP REMOVE L4 (24 DUPLICATES REMOVED) |
| L8 | 1 | S L7 AND RAT |
| L9 | 1010 | S RAT IGE |
| L10 | 0 | S L9 AND CH3 DOMAIN |
| L11 | 7 | S L4 AND CH2 DOMAIN |
| L12 | 3 | DUP REMOVE L11 (4 DUPLICATES REMOVED) |

=> s l4 and CH4 domain
L13 11 L4 AND CH4 DOMAIN

=> dup remove l13
PROCESSING COMPLETED FOR L13
L14 4 DUP REMOVE L13 (7 DUPLICATES REMOVED)

=> d l14 1-4 cbib abs

L14 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2002 ACS
2002:272796 Document No. 136:293510 Anti-allergic vaccines comprising peptides of Fc portion of **IgE** .epsilon. heavy chain and carrier protein. Morsey, Mohamad Ali; Sheppard, Michael George; Wheeler, David Walter (Pfizer Products Inc., USA). Eur. Pat. Appl. EP 1195161 A2 20020410, 38 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 2001-307247 20010824. PRIORITY: US 2000-PV228989 20000830.
AB The present invention provides compns. and methods for the use of antigenic peptides derived from the Fc portion of the epsilon heavy chain of an **IgE** mol. as vaccines for the treatment and prevention of **IgE**-mediated allergic disorders. In particular, the invention provides compns., methods for the treatment and prevention of **IgE** -mediated allergic disorders comprising an immunogenic amt. of one or more antigenic peptides derived from the **CH3 domain** or junction of Ch-3/**CH4 domain** of an **IgE** mol.

and methods for the evaluation of **IgE** mediated allergies in dogs. The allergic disorder is asthma, allergic rhinitis, gastrointestinal allergy, food allergy, eosinophilia, conjunctivitis, or glomerular nephritis. The vaccine compns. may also comprises carrier protein such as KLH, PhoE, rmLT, TraT and gD from BhV-1 virus; and adjuvant such as aluminum hydroxide, monophosphoryl lipid A, Thr-MDP, immunostimulatory oligonucleotide, cytokine, interleukin 12, interleukin 2, interleukin 1, saponin, cholera toxin, heat labile toxin, etc.

L14 ANSWER 2 OF 4 MEDLINE DUPLICATE 1

94097359 Document Number: 94097359. PubMed ID: 7505881. Epitope mapping of the site(s) of binding of Fc epsilon RII/CD23 within human **IgE** . Determination of the B lymphocyte-binding sites by use of synthetic peptides and anti-peptide antibodies representative of linear Fc sequences. Ghaderi A A; Stanworth D R. (Department of Microbiology and Immunology, Shiraz University of Medical Science, Iran. ) MOLECULAR IMMUNOLOGY, (1993 Dec) 30 (18) 1655-63. Journal code: 7905289. ISSN: 0161-5890. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The work undertaken has investigated the structure-function relationship between **IgE** and its low affinity receptor on B lymphocytes. To identify sites on the **IgE** molecule which interact with the low affinity receptor (Fc epsilon RII/CD23), 10 different peptide sequences within the CH2, CH3 and **CH4 domains** of human **IgE** were selected according to charge, overall hydrophobicity and possible accessibility on native **IgE** sequences. Peptides representative of these were synthesized by the solid phase procedure; and their cytophilic activities were examined by determining their capacity to inhibit the binding of radiolabelled or erythrocyte-bound **IgE** to a Fc epsilon RII/CD23 positive B cell line (RPMI-8866). Moreover, these linear sequences were rendered immunogenic by conjugation to a protein carrier (KLH) and used to produced polyclonal antibodies in rabbits. The reactivity of the anti-peptide antibodies with both free peptides and native **IgE** bound to a solid phase, as well as their capacity to inhibit binding of **IgE** to a Fc epsilon RII/CD23 positive cell line, were investigated. Results from such use of peptides and anti-peptide antibodies indicate that two sequences, representative of residues 364-383 and 401-415, could be involved in the binding of **IgE** to both membrane-bound and soluble form Fc epsilon RII/CD23; indicating that the B lymphocyte-binding site on human **IgE** may be restricted to the **CH3 domain**.

L14 ANSWER 3 OF 4 MEDLINE DUPLICATE 2

89009864 Document Number: 89009864. PubMed ID: 2459242. A monoclonal anti-**IgE** antibody against an epitope (amino acids 367-376) in the **CH3 domain** inhibits **IgE** binding to the low affinity **IgE** receptor (CD23). Chretien I; Helm B A; Marsh P J; Padlan E A; Wijdenes J; Banchereau J. (UNICET, Laboratory for Immunological Research, Dardilly, France. ) JOURNAL OF IMMUNOLOGY, (1988 Nov 1) 141 (9) 3128-34. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB We have produced three different mAb specific for human **IgE**-Fc. Their binding pattern to either heat-denatured **IgE** or a family of overlapping **IgE**-derived recombinant peptides and their ability to affect interaction of **IgE** with its low affinity receptor Fc epsilon R2/CD23 demonstrate that they recognize distinct epitopes on the **IgE** molecule. All three mAb were able to induce basophil degranulation as measured by the induction of histamine release. mAb 173 recognizes a thermolabile epitope in the **CH4 domain**. It does not affect the binding of **IgE** to Fc epsilon R2/CD23. mAb 272 recognizes a thermostable epitope that maps to a sequence of 36 amino acids (AA) spanning part of the CH2 and **CH3 domain** and it does not affect the binding of **IgE** to Fc epsilon R2/CD23. mAb 27 recognizes a thermolabile epitope located on a 10

AA stretch (AA 367-376) in the **CH3 domain**. This area contains one N-linked oligosaccharide (Asn-371), but the antibody is not directed against carbohydrate because it binds to Escherichia coli-derived **IgE** peptides. mAb 27 inhibits the binding of **IgE** to Fc epsilon R2/CD23 but is still capable of reacting with **IgE** already bound to Fc epsilon R2/CD23. These data suggest that upon binding to Fc epsilon R2/CD23, the **IgE** molecule engages one of two equivalent-binding sites close to the glycosylated area of the **CH3 domain**.

L14 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2002 ACS
1986:146780 Document No. 104:146780 Localization of epitopes of IgG Fc responsible for antibody-dependent cell-mediated cytotoxicity. Gergely, J.; Sarmay, J. (Sect. Immunol., Univ. Lajos Eotvos, Budapest, Hung.). Immunologiya (Moscow) (5), 27-30 (Russian) 1985. CODEN: IMUNDA. ISSN: 0206-4952.
AB Ig Fc-receptors (FcR) of human lymphocytes are of two types: monomeric receptors (FcR-I) having a mol. wt. of 60,000 daltons, and polymeric, membrane-fixed receptors (FcR-II). By studying the inhibitory effects of various synthetic peptides (corresponding to parts of the CH2- and **CH3-domains** of IgG and part of the **CH4-domain** of **IgE**) on antibody-dependent cell-mediated cytotoxicity, it was concluded that sequences interacting with one of the FcR-II binding sites are located in the CH2-domain Lys274-Arg301 and in the **CH3-domain** Ser408-Arg416.

=> s CH2 and CH3 of IgE
L15 0 CH2 AND CH3 OF IGE

=> s IgE
L16 108337 IGE

=> s l16 and opossum
L17 13 L16 AND OPOSSUM

=> dup remove l17
PROCESSING COMPLETED FOR L17
L18 5 DUP REMOVE L17 (8 DUPLICATES REMOVED)

=> d l18 1-5 cbib abs

L18 ANSWER 1 OF 5 MEDLINE
2002300838 Document Number: 22035325. PubMed ID: 11967231. Generation of therapeutic antibody responses against **IgE** through vaccination. Vernersson Molly; Ledin Anna; Johansson Jeannette; Hellman Lars. (Department of Cell and Molecular Biology, Biomedical Center, University of Uppsala, S-751 24 Uppsala, Sweden. ) FASEB JOURNAL, (2002 Jun) 16 (8) 875-7. Journal code: 8804484. ISSN: 1530-6860. Pub. country: United States. Language: English.
AB **IgE** is the central mediator in atopic allergies such as hay fever, eczema, and asthma; therefore, it is a prime target in the development of allergen-independent preventive treatments. We describe an active immunization strategy that has the potential to reduce **IgE** to a clinically significant extent. The active vaccine component is a chimeric **IgE** molecule, Cepsilon2-Cepsilon3-Cepsilon4. The receptor-binding target domain, Cepsilon3, is derived from the recipient species, whereas the flanking domains, Cepsilon2 and Cepsilon4, are derived from an evolutionarily distant mammal. The flanking domains have dual functions, acting both as structural support for the Cepsilon3 domain and to break T cell tolerance by providing foreign T cell epitopes. The efficacy of the vaccine was studied in an ovalbumin-sensitized rat model. Vaccination resulted in antibody responses against **IgE** in all

rats and in a substantial reduction in serum **IgE** levels in three out of four strains. The skin reactivity upon allergen challenge was significantly reduced in vaccinated animals. The vaccine appears to be safe to use as an antigen. No cross-linking activity was observed in sera of vaccinated animals, and the response to vaccination was reversible with time. Our results suggest that active immunization against **IgE** has the potential to become a therapeutic method for humans.

L18 ANSWER 2 OF 5 SCISEARCH COPYRIGHT 2002 ISI (R)
2000:406421 The Genuine Article (R) Number: 317HU. Immunoglobulin genetics of marsupials. Miller R D (Reprint); Belov K. UNIV NEW MEXICO, DEPT BIOL, ALBUQUERQUE, NM 87131 (Reprint); MACQUARIE UNIV, DEPT SCI BIOL, N RYDE, NSW 2109, AUSTRALIA. DEVELOPMENTAL AND COMPARATIVE IMMUNOLOGY (JUL 2000) Vol. 24, No. 5, pp. 485-490. Publisher: PERGAMON-ELSEVIER SCIENCE LTD. THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND. ISSN: 0145-305X. Pub. country: USA; AUSTRALIA. Language: English.
*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB Until recently, studies of marsupial immunoglobulins were limited to primarily protein analyses, such as Protein A binding and immunological cross-reactivity to eutherian immunoglobulins to draw conclusions about the isotypes present in metatherians. This left an interesting gap in our knowledge of the evolution of vertebrate, more specifically mammalian, antibodies and provided little insight into the diversity of marsupial antibodies. Recently, however, there has been a flurry of papers from multiple laboratories describing, at the molecular level, the heavy and light chain classes present in marsupials with some analysis of the expressed repertoires. These studies have provided the evidence to determine when some of the uniquely mammalian isotypes, e.g. IgG and **IgE**, appeared in evolution, and are a first look at the complexity of heavy and light chain variable regions in a metatherian. Here we review what was known prior to the cloning of marsupial Ig genes and what we have learned recently. (C) 2000 Elsevier Science Ltd. All rights reserved.

L18 ANSWER 3 OF 5 MEDLINE
2000150240 Document Number: 20150240. PubMed ID: 10684965. Molecular cloning of the brushtail possum (Trichosurus vulpecula) immunglobulin E heavy chain constant region. Belov K; Harrison G A; Miller R D; Cooper D W. (CRC for Conservation and Management of Marsupials, School of Biological Sciences, Macquarie University, North Ryde, Australia. ) MOLECULAR IMMUNOLOGY, (1999 Dec) 36 (18) 1255-61. Journal code: 7905289. ISSN: 0161-5890. Pub. country: ENGLAND: United Kingdom. Language: English.
AB The immunobiology of marsupial **IgE** is poorly understood. As a first step towards the development of immunological reagents for marsupials and to obtain a further understanding of immunoglobulin evolution, a brushtail possum (Trichosurus vulpecula) mesenteric lymph node cDNA library was screened for the heavy chain constant region of **IgE** (Cepsilon), using a partial Cepsilon probe from the American marsupial, Monodelphis domestica. The cDNA sequence for T. vulpecula Cepsilon was determined and found to be most similar to the M. domestica Cepsilon sequence [(76%) at the amino acid level]. T. vulpecula Cepsilon has amino acid sequence similarities ranging from 43-52% with various eutherian Cepsilon sequences. The secondary structure of T. vulpecula Cepsilon, based on loops formed by internal disulfide bonds, more closely resembles rodent Cepsilon than the American marsupial sequence.

L18 ANSWER 4 OF 5 MEDLINE DUPLICATE 1
2000043989 Document Number: 20043989. PubMed ID: 10579388. Cloning and structural analysis of IgM (mu chain) and the heavy chain V region repertoire in the marsupial Monodelphis domestica. Aveskogh M; Pilstrom L; Hellman L. (Department of Cell and Molecular Biology, University of Uppsala, Biomedical Center, Sweden. ) DEVELOPMENTAL AND COMPARATIVE IMMUNOLOGY, (1999 Oct-Dec) 23 (7-8) 597-606. Journal code: 7708205. ISSN: 0145-305X. Pub. country: United States. Language: English.

AB To address the question of the Ig isotype repertoire of non placental mammals, we have examined the Ig expression in the marsupial Monodelphis domestica (grey short tailed **opossum**). Screening of an **opossum** spleen cDNA library has previously led to the isolation of full length clones for **opossum** IgG (gamma chain), **IgE** (epsilon chain) and IgA (alpha chain). We now present the isolation of several cDNA clones encoding the entire constant regions of the **opossum** IgM (mu chain). A comparative analysis of the amino acid sequences for IgM from various animal species showed that **opossum** IgM, within the various animals studied, is the most divergent member of its Ig class. However, it still conforms to the general structure of IgM in other vertebrates. Four Ig classes have now been identified in **opossum** and only one isotype is apparently present within each Ig class, IgM, IgG, IgA and **IgE**. **Opossum** has previously been shown to have a limited VH region diversity, with only two V gene families. Both of these belong to the group III of mammalian VH sequences. This limitation in variability is to some extent compensated for by a large variation in D, P and N regions, both in size and in sequence. However, evidence for the expression of only two functional J segments has so far been detected, which indicates a rather limited diversity also of the J segments in the **opossum**.

L18 ANSWER 5 OF 5 MEDLINE DUPLICATE 2
1998425532 Document Number: 98425532. PubMed ID: 9754561. Evidence for an early appearance of modern post-switch isotypes in mammalian evolution; cloning of **IgE**, IgG and IgA from the marsupial Monodelphis domestica. Aveskogh M; Hellman L. (Department of Medical Biochemistry and Microbiology, University of Uppsala, Sweden. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (1998 Sep) 28 (9) 2738-50. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB In birds, reptiles and amphibians the IgY isotype exhibits the functional characteristics of both of IgG and **IgE**. Hence, the gene for IgY most likely duplicated some time during early mammalian evolution and formed the ancestor of present day IgG and **IgE**. To address the question of when IgY duplicated and formed two functionally distinct isotypes, and to study when IgG and IgA lost their second constant domains, we have examined the Ig expression in a non-placental mammal, the marsupial Monodelphis domestica (grey short-tailed **opossum**). Screening of an **opossum** spleen cDNA library revealed the presence of all three isotypes in marsupials. cDNA clones encoding the entire constant regions of **opossum IgE** (epsilon chain), IgG (gamma chain) and IgA (alpha chain) were isolated, and their nucleotide sequences were determined. A comparative analysis of the amino acid sequences for IgY, IgA, **IgE** and IgG from various animal species showed that **opossum IgE**, IgG and IgA on the phylogenetic tree form branches clearly separated from their eutherian counterparts. However, they still conform to the general structure found in eutherian **IgE**, IgG and IgA. Our findings indicate that all the major evolutionary changes in the Ig isotype repertoire, and in basic Ig structure that have occurred since the evolutionary separation of mammals from the early reptile lineages, occurred prior to the evolutionary separation of marsupials and placental mammals.

```
=> s platypus IgE
L19          0 PLATYPUS IGE

=> s platypus
L20       1597 PLATYPUS

=> s l20 and IgE
L21          0 L20 AND IGE
```

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 80.13 | 80.34 |
| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
| CA SUBSCRIBER PRICE | -4.34 | -4.34 |

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| NEWS 5 | Feb 19 | Access via Tymnet and SprintNet Eliminated Effective 3/31/02 |
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| NEWS 8 | Mar 22 | TRCTHERMO no longer available |
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                                                       ENTRY    SESSION
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=> s CH2 domain
L1          756 CH2 DOMAIN

=> s l1 and IgE
L2           32 L1 AND IGE

=> s l2 and fused
L3            0 L2 AND FUSED

=> s l2 and fusion
L4            1 L2 AND FUSION

=> d l4 cbib abs

L4   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
1999:311111   Document No. 130:336963  Methods and compositions comprising
     glycoprotein glycoforms.  Raju, T. Shantha (Genentech, Inc., USA).  PCT
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Int. Appl. WO 9922764 A1 19990514, 52 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US21925 19981016. PRIORITY: US 1997-962497 19971031.

AB This invention relates to novel glycoprotein glycoform prepns. comprising the substantially homogeneous glycoprotein glycoforms and combinations thereof. More particularly the invention relates to glycoprotein prepns. comprising a particular Fc glycoforms and methods for producing, detecting, enriching and purifying the glycoforms. The invention further relates to Igs and esp. antibodies comprising a **CH2 domain** having particular N-linked glycans. The antibody is a monoclonal antibody, IgG, IgG1 specific for CD20, HER2, VEGF, **IgE**, or an immunoadhesin glycoprotein such as tumor necrosis factor-IgG1 chimera. The compn. is prepd. by reacting substrate glycoprotein in aq. buffered soln. contg. metal salt, activated galactose, galactosyltransferase, and recovering the glycoprotein. The compn. is esp. useful for cancer treatment.

```
=> s self IgE domain
L5            0 SELF IGE DOMAIN

=> s IgE domains
L6            4 IGE DOMAINS

=> s l6 and self or noneself
L7            0 L6 AND SELF OR NONESELF

=> dup remove l6
PROCESSING COMPLETED FOR L6
L8            4 DUP REMOVE L6 (0 DUPLICATES REMOVED)

=> d l8 1-4 cbib abs

L8   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2002 ACS
1991:79797   Document No. 114:79797  Mapping of the high affinity Fc.epsilon.
     receptor binding site to the third constant region domain of IgE.  Nissim,
     Ahuva; Jouvin, Marie Helene; Eshhar, Zelig (Dep. Chem. Immunol., Weizmann
     Inst. Sci., Rehovot, 76100, Israel).  EMBO J., 10(1), 101-7 (English)
     1991.  CODEN: EMJODG.  ISSN: 0261-4189.
AB   Identification of the precise region(s) on the IgE mol. that take part in
     the binding of IgE to its high affinity receptor (Fc.epsilon.RI) may lead
     to the design of IgE analogs able to block the allergic response.  To
     localize the Fc.epsilon.RI-binding domain of mouse IgE, the authors
     attempted to confer on human IgE, which normally does not bind to the
     rodent receptor, the ability to bind to the rat Fc.epsilon.RI.  Employing
     exon shuffling, they have expressed chimeric .epsilon.-heavy chain genes
     composed of a mouse (4-hydroxy-3-nitrophenyl)acetic acid (NP)-binding VH
     domain, and human C.epsilon. in which various domains were replaced by
     their murine counterparts.  This has enabled one to test the
     Fc.epsilon.RI-binding of each mouse IgE domain while maintaining the
     overall conformation of the mol.  All of the chimeric IgE mols. which
     contain the murine C.epsilon.3, bound equally to both the rodent and human
     receptor, as well as to monoclonal antibodies recognizing a site on IgE
     which is identical or very close to the Fc.epsilon.RI binding site.
     Deletion of the second const. region domain did not impair either the
     binding capacity of the mutated IgE or its ability to mediate mast cell
     degrdn.  These results assign the third epsilon domain of IgE as the
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principal region involved in the interaction with the Fc.epsilon.RI.

L8 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2002 ACS
1987:475759 Document No. 107:75759 Analysis of the interaction between rat immunoglobulin E and rat mast cells using anti-peptide antibodies. Burt, David S.; Hastings, Gillian Z.; Healy, John; Stanworth, Denis R. (Dep. Immunol., Univ. Birmingham, Birmingham, B15 2TJ, UK). Mol. Immunol., 24(4), 379-89 (English) 1987. CODEN: MOIMD5. ISSN: 0161-5890.
AB Polyclonal antisera with predetd. specificities for a range of rat IgE epitopes were produced by immunizing rabbits with keyhole limpet hemocyanin-conjugates of 5 different synthetic peptides representing sequences 378-396, 414-428, 491-503, 522-535 and 560-571 in the CH3 and CH4 domains of rat IgE. Each rabbit elicited peptide-specific antibodies which were capable of binding affinity-purified rat IgE and IgE in rat immunocytoma serum. Heating a soln. of rat IgE at 56.degree. for 1 h, a treatment known to abolish the cytophilic activity of rat IgE and also induce irreversible conformational changes in the CH3 and CH4 domains, resulted in enhanced binding of the Ig to antibodies directed against IgE sequences represented by 2 of the synthetic peptides, 414-428 and 491-503, but not to the 3 other peptides. The 5 anti-peptide sera together with 2 previously studied antisera specific for rat IgE sequence 459-472 and 542-557 were tested in functional assays designed to investigate the mode of interaction between rat IgE and its receptor on rat mast cells. Each anti-peptide serum was capable of inhibiting the binding of IgE to mast cells and able to initiate the secretion of histamine from cells sensitized with rat IgE in an anti-IgE-induced manner. Based on the evidence implicating the CH3 and/or CH4 domains as the location of the mast cell receptor-site on rat IgE, a model to describe the mode of interaction between IgE and its mast cell receptor is suggested.

L8 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS
1986:205156 Document No. 104:205156 Thermoinactivation of human IgE: antigenic and functional modifications. Demuelemester, C.; Weyer, A.; Peltre, G.; Laurent, M.; Marchand, F.; David, Bernard (Lab. Immuno-Allergie, Inst. Pasteur, Paris, 75724/15, Fr.). Immunology, 57(4), 617-20 (English) 1986. CODEN: IMMUAM. ISSN: 0019-2805.
AB The thermoinactivation kinetics of IgE were studied in exptl. models revealing the antigenic properties and the basophil-sensitizing capacity of these Igs. A pool of human sera contg. anti-Dactylis glomerata (Dg) IgE was heated from 5 min up to 4 h at 56.degree.. The IgE antigenicity was tested by 2 polyclonal 125I-labeled anti-IgE antibodies; one anti-IgE was specific of the whole Fc.epsilon. region, while the other had a specificity restricted to the D.epsilon.2 domain. Radioimmunoassays showed that the D.epsilon.2 epitopes were more rapidly altered than the D.epsilon.1 epitopes. The capacity of IgE to bind to basophil Fc.epsilon. receptors was assayed by passive sensitization expts. Basophil sensitivity towards the Dg pollen ext. was tested by histamine release expts. in the presence of this allergen. A progressive decrease in cell sensitivity was obsd. when IgE samples used for cell sensitization were heated for >5 min. Thermoinactivation kinetics of IgE revealed an unexpected increase in the apparent quantity and biol. activity of IgE heated for 5 min at 56.degree.. This could be due to auto-anti-IgE antibodies linked to the unheated IgE which interfere with the biol. activities of IgE and their quantification.

L8 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2002 ACS
1983:420734 Document No. 99:20734 Structural studies on the membrane-bound immunoglobulin E-receptor complex. 1. Characterization of large plasma membrane vesicles from rat basophilic leukemia cells and insertion of amphipathic fluorescent probes. Holowka, David; Baird, Barbara (Dep. Chem., Cornell Univ., Ithaca, NY, 14853, USA). Biochemistry, 22(14), 3466-74 (English) 1983. CODEN: BICHAW. ISSN: 0006-2960.
AB In order to investigate the properties of the membrane-bound IgE-receptor

complex, a single procedure has been adapted for prepg. large plasma membrane vesicles from rat basophilic leukemia cells. These vesicles pinch off from the adherent cells after treatment with 2 mM N-ethylmaleimide or 50 mM formaldehyde and 1 mM dithiothreitol, and they are isolated from the supernatant after 2 centrifugation steps with yields of 20-25% of the initial cell-bound 125I-labeled IgE. With phase and fluorescence microscopy, micron-size vesicles are seen which are unilamellar and spherically shaped and devoid of intracellular organelles. On dextran gradients at least 70% of the 125I-labeled IgE is bound to membranes which band at low d., indicating large, intact vesicles that are impermeable to macromols. Between 60 and 75% of the bound 125I-labeled IgE is accessible to the external medium, showing the vesicles to be predominately right side out. This prepn. was suitable for resonance energy-transfer measurements. The amphipathic, fluorescent donor and acceptor probes partition into the vesicle bilayer in a randomly distributed, noninteracting manner. The densities of the probes can be ascertained directly from the amt. of energy transfer that is obsd. as a function of acceptor concn.

=> s nonplacental mammal
L9 17 NONPLACENTAL MAMMAL

=> s l9 and IgE
L10 1 L9 AND IGE

=> d l10 cbib abs

L10 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
1999:817308 Document No. 132:292442 Cloning and structural analysis of IgM (.mu. chain) and the heavy chain V region repertoire in the marsupial Monodelphis domestica. Aveskogh, Maria; Pilstrom, Lars; Hellman, Lars (Department of Cell and Molecular Biology, University of Uppsala, Uppsala, S-751 24, Swed.). Developmental & Comparative Immunology, 23(7-8), 597-606 (English) 1999. CODEN: DCIMDQ. ISSN: 0145-305X. Publisher: Elsevier Science Ltd..
AB To address the question of the Ig isotype repertoire of **nonplacental mammals**, the authors have examd. the Ig expression in the marsupial Monodelphis domestica (gray short tailed opossum). Screening of an opossum spleen cDNA library has previously led to the isolation of full length clones for opossum IgG (.gamma. chain), **IgE** (.epsilon. chain) and IgA (.alpha. chain). The authors now present the isolation of several cDNA clones encoding the entire const. regions of the opossum IgM (.mu. chain). A comparative anal. of the amino acid sequences for IgM from various animal species showed that opossum IgM, within the various animals studied, is the most divergent member of its Ig class. However, it still conforms to the general structure of IgM in other vertebrates. Four Ig classes have now been identified in opossum and only one isotype is apparently present within each Ig class, IgM, IgG, IgA and **IgE**. Opossum has previously been shown to have a limited VH region diversity, with only two V gene families. Both of these belong to the group III of mammalian VH sequences. This limitation in variability is to some extent compensated for by a large variation in D, P and N regions, both in size and in sequence. However, evidence for the expression of only two functional J segments has so far been detected, which indicates a rather limited diversity also of the J segments in the opossum.

=> s whale
L11 20566 WHALE

=> s l11 and IgE

L12 9 L11 AND IGE

=> dup remomve l12
ENTER REMOVE, IDENTIFY, ONLY, OR (?):only
'REMOMVE' IS VALID ONLY WITH THE REMOVE OPTION
File names can only be entered when using the REMOVE option of the DUPLICATE command.

=> dup remove l12
PROCESSING COMPLETED FOR L12
L13 6 DUP REMOVE L12 (3 DUPLICATES REMOVED)

=> s l13 and CH2 domain
L14 0 L13 AND CH2 DOMAIN

=> d l13 1-6 cbib abs

L13 ANSWER 1 OF 6 MEDLINE DUPLICATE 1
2001085438 Document Number: 21013913. PubMed ID: 11130147. [Eosinophilic esophagitis associated with recurrent urticaria: is the worm Anisakis simplex involved?]. Eosinophile Osophagitis assoziiert mit rezidivierender Urtikaria: Steckt da der Wurm Anisakis simplex drin?. Bircher A J; Gysi B; Zenklusen H R; Aerni R. (Allergologische Poliklinik, Dermatologische Universitatsklinik, Kantonsspital Basel.. Andreas.Bircher@unibas.ch) . SCHWEIZERISCHE MEDIZINISCHE WOCHENSCHRIFT. JOURNAL SUISSE DE MEDECINE, (2000 Nov 25) 130 (47) 1814-9. Journal code: 0404401. ISSN: 0036-7672. Pub. country: Switzerland. Language: German.
AB Anisakis simplex, a fish parasite of the nematode family, typically infects marine mammals such as **whales**, dolphins and seals. Human anisakiasis, which is acquired by eating raw or insufficiently heated fish or squid, has gained world-wide importance. Infestation with living larvae caused by eating parasitised fish results in acute upper abdominal pain, nausea and vomiting and may be confused with acute abdomen due to appendicitis and other inflammatory abdominal disorders. Extraintestinal organ manifestations are rare. Endoscopically, inflammation, oedema, erosions and ulcerations may be found. The parasite can been found in up to 50% of patients. Histologically, an eosinophilic inflammation is typical. Acute anisakiasis may be prevented by thorough cooking or deep-freezing the parasitised fish for at least 48 h. IgG-antibodies specific for Anisakis simplex are thought to represent an immunological host reaction against parasitic antigens. More recently, allergic reactions to Anisakis ingestion or exposure, such as urticaria, anaphylaxis and even occupational asthma, have been reported. These allergic reactions may also occur when the fish has been properly cooked, and hence these allergens are thought to be heat-stable. Such cases may be diagnosed by skin tests and the determination of specific Anisakis-**IgE**. However, the specificity of **IgE** is low, since they may also be present in exposed asymptomatic individuals. Since the eliciting allergens are temperature-stable, prophylactic dietetic measures are indicated. We report a case from Switzerland acquired during a holiday in Portugal. The patient suffered from recurrent dysphagia and urticaria, and histologically eosinophilic oesophagitis was found. IgG-antibodies and a positive skin prick test to Anisakis simplex support its aetiologic role for the symptoms.

L13 ANSWER 2 OF 6 SCISEARCH COPYRIGHT 2002 ISI (R)
97:772220 The Genuine Article (R) Number: YA588. In vivo and in vitro immunomodulation induced by the extract of the mycelium fungus Polyporus squamosus. Babakhin A A (Reprint); Majoul L A; Vedernikov A A; Leskov V P; Pisarev V M; Babakhin A A; Logina N Y; Gushchin I S; Nolte H; DuBuske L M. NATL RES CTR, INST IMMUNOL, 24-2 KASHIRSKOYE SHOSSE, MOSCOW 115478, RUSSIA (Reprint). ALLERGY AND ASTHMA PROCEEDINGS (SEP-OCT 1997) Vol. 18, No. 5, pp. 301-310. Publisher: OCEAN SIDE PUBLICATIONS INC. 95 PITMAN ST,

PROVIDENCE, RI 02906. ISSN: 1088-5412. Pub. country: RUSSIA. Language: English.
*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB The mycelial mass of the fungus Polyporus Squamosus strain 64 (PS-64) was disintegrated by mechanical and ultrasound treatments. After centrifugation, the supernatant containing the disintegrate was dialyzed and lyophilized. The resultant PS-64 extract was subsequently investigated as an immunomodulator of **IgE** and IgG responses to ovalbumin (OA) in (CBAxC57BL/6)F1 mice using passive cutaneous anaphylaxis (PCA) and enzyme-linked immunosorbent assay (ELISA), respectively. Multiple injections of PS-64 extract in doses of 1.5, 15, and 150 mg/kg administered before the primary or secondary immunization of mice with OA resulted in a dose-dependent inhibition of both **IgE** and IgG antibody responses to OA. In contrast to the inhibition of the anti-OA **IgE** response noted during the entire 3-week observation period the anti-OA IgG response was restored to control level by the third week of secondary immunization. The glass microfiber-based whole blood histamine release assay demonstrated that various concentrations of the PS-64 extract did not influence histamine release induced either by anti-**IgE** or by specific allergens from basophils derived from **whale** blood of allergen-sensitized patients. Using the hemolytic plaque assay significant suppression of IgM-secreting cell formation was noted in (CBAxC57BL/6)F1 mice administered various doses of the PS-64 extract before immunization. The PS-64 extract inhibited the in vitro proliferation of human mononuclear cells upon stimulation with phytohemagglutinin (PHA). In a dose-dependent manner the PS-64 extract also inhibited delayed-type hypersensitivity reaction and skin graft rejection, similar to the effect noted with usage of Cyclosporin A (CsA) in (CBAxC57BL/6)F1 mice. Our investigation suggests that the immunomodulatory effects of PS-64 should be studied further for potential clinical therapeutic utility.

L13 ANSWER 3 OF 6 SCISEARCH COPYRIGHT 2002 ISI (R)

97:333811 The Genuine Article (R) Number: WV713. Induction of an epitope-specific humoral immune response by lipopeptide-hapten conjugates: Enhancement of the anti-melittin response by a synthetic T helper (T-h)-cell epitope. Hoffmann P (Reprint); Loleit M; Mittenbuhler K; Beck W; Wiesmuller K H; Jung G; Bessler W G. UNIV FREIBURG, INST IMMUNOBIOL, STEFAN MEIER STR 8, D-79104 FREIBURG, GERMANY (Reprint); UNIV TUBINGEN, INST ORGAN CHEM, D-72076 TUBINGEN, GERMANY; UNIV TUBINGEN, NMI, D-72762 REUTLINGEN, GERMANY. FEMS IMMUNOLOGY AND MEDICAL MICROBIOLOGY (APR 1997) Vol. 17, No. 4, pp. 225-234. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0928-8244. Pub. country: GERMANY. Language: English.
*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Lipopeptides of bacterial origin constitute potent immunoadjuvants when combined with antigens. After the immunization with lipopeptides covalently coupled to non-immunogenic low-molecular-mass antigens or haptens, a hapten-specific humoral immune response can often be obtained. The response against synthetically prepared melittin fragments was further enhanced by the additional introduction of a T helper (T-h)-cell epitope into the lipopeptide-hapten conjugate. The T-h-cell epitope applied, which is presented by the MHC class II molecule of the BALB/c (H-2(d)) haplotype, consisted of a synthetic 16-amino-acid oligopeptide derived from sperm **whale** myoglobin. The immune-enhancing effect was most pronounced for the melittin-derived peptide fragments [Mel(1-16)] and [Mel(17-26)-CONH2], Antibodies obtained after 3 immunizations with the conjugates recognized the synthetic as well as the native melittin molecule. Our results show that it is possible to markedly enhance a weak hapten-specific immune response by coupling the haptens to a lipopeptide conjugated to a haplotype-specific T helper-cell epitope. The novel conjugates are well suited for the optimization of immunization procedures, and for the development of novel synthetic vaccines.

L13 ANSWER 4 OF 6 SCISEARCH COPYRIGHT 2002 ISI (R)
96:123732 The Genuine Article (R) Number: TU692. T-CELL-DERIVED IL-3 INDUCES THE PRODUCTION OF IL-4 BY NON-B-CELL, NON-T-CELL TO AMPLIFY THE TH2-CYTOKINE RESPONSE TO A NON-PARASITE ANTIGEN IN SCHISTOSOMA-MANSONI-INFECTED MICE. KULLBERG M C (Reprint); BERZOFSKY J A; JANKOVIC D L; BARBIERI S; WILLIAMS M E; PERLMANN P; SHER A; TROYEBLOMBERG M. UNIV STOCKHOLM, DEPT IMMUNOL, S-10691 STOCKHOLM, SWEDEN (Reprint); NIAID, NIH, PARASIT DIS LAB, IMMUNOBIOL SECT, BETHESDA, MD, 20892; NCI, METAB BRANCH, MOLEC IMMUNOGENET & VACCINE RES SECT, NIH, BETHESDA, MD, 20892; NIAID, NIH, BIOL RES BRANCH, BETHESDA, MD, 20892. JOURNAL OF IMMUNOLOGY (15 FEB 1996) Vol. 156, No. 4, pp. 1482-1489. ISSN: 0022-1767. Pub. country: SWEDEN; USA. Language: ENGLISH.
*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB We describe a novel amplification mechanism underlying the increased early IL-4 production observed in Schistosoma mansoni-infected mice in response to a non-parasite Ag, sperm **whale** myoglobin (SwMb). Earlier studies have shown that splenic Fc epsilon R(+) non-B, non-T (NBNT) cells from schistosome-infected mice secrete IL-4 after stimulation with parasite Ag. We now demonstrate that purified NBNT cells from SwMb-immunized S. mansoni-infected mice do not respond directly to SwMb, but produce IL-4 in response to IL-3. Accordingly, we show that the early SwMb-specific IL-4 response of spleen cells (SC) from immunized infected mice is dependent on IL-3 and on CD4(+) T cells. Thus, most of the early SwMb-induced IL-4 from SC of infected mice appears to be produced by NBNT cells triggered by IL-3 synthesized by SwMb-specific CD4(+) T cells. IL-3-induced IL-4 production was also observed in purified NBNT cells from immunized uninfected mice, but the frequency and/or IL-4-producing capacity of splenic IL-3-responsive cells was found to be 8 to 16 times higher in immunized infected animals, IL-4 production by purified CD4(+) cells from immunized infected mice was also seen after SwMb stimulation, but this response showed slower kinetics than those of total SC, was IL-3-independent, and on average threefold greater than that by CD4(+) cells from immunized uninfected controls. Thus, increased SwMb-induced IL-4 production in immunized S. mansoni-infected mice results from direct synthesis by CD4(+) T cells, as well as their stimulation via IL-3 of an expanded population of NBNT cells. The latter pathway may serve as an amplification loop for Th2-cytokine responses.

L13 ANSWER 5 OF 6 SCISEARCH COPYRIGHT 2002 ISI (R)
92:320022 The Genuine Article (R) Number: HU686. INFECTION WITH SCHISTOSOMA-MANSONI ALTERS TH1/TH2 CYTOKINE RESPONSES TO A NON-PARASITE ANTIGEN. KULLBERG M C; PEARCE E J; HIENY S E; SHER A; BERZOFSKY J A (Reprint). NCI, METAB BRANCH, MOLEC IMMUNOGENET & VACCINE RES SECT, BETHESDA, MD, 20892; NIAID, PARASIT DIS LAB, IMMUNOL & CELL BIOL SECT, BETHESDA, MD, 20892. JOURNAL OF IMMUNOLOGY (15 MAY 1992) Vol. 148, No. 10, pp. 3264-3270. ISSN: 0022-1767. Pub. country: USA. Language: ENGLISH.
*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Schistosoma mansoni infection in the mouse has been shown to be accompanied by a down-regulation in parasite-Ag- and mitogen-induced Th1 cytokine secretion (IL-2 and IFN-gamma) with a simultaneous increase in the production of Th2 cytokines (IL-4, IL-5, and IL-10), suggesting a generalized imbalance in lymphocyte function. In the present study, we examined whether infection with S. mansoni would also influence the character of immune responses to a non-parasite Ag, sperm **whale** myoglobin (SwMb). When spleen cells (SC) from schistosome-infected SwMb-immunized animals were stimulated with SwMb, their production of IL-2 and IFN-gamma per CD4+ cell was found to be significantly reduced (by 45% and 59%, respectively) compared with the responses observed in immunized uninfected animals. Moreover, SwMb-induced secretion of IL-4 per CD4+ cell was increased threefold in SC cultures from infected mice. No myoglobin-induced IL-5 was detected in the same cultures. Addition to SC cultures of a neutralizing mAb specific for IL-10 partly restored the

suppressed IFN-gamma response to SwMb seen in infected mice, suggesting a role for IL-10 in the observed down-regulation. S. mansoni-infected mice also showed an impaired antibody response to SwMb, with levels ranging from 10% to 27% of those observed in uninfected mice, although no differences in IgG isotype were evident. Taken together, these results suggest that infection with S. mansoni induces a down-regulation of Th1 responses and elevation of Th2 responses to unrelated foreign immunogens as well as to parasite Ag themselves. One implication of these findings is that helminth-infected individuals may have altered cell-mediated immune function to other microbial agents.

L13 ANSWER 6 OF 6 SCISEARCH COPYRIGHT 2002 ISI (R)
92:623249 The Genuine Article (R) Number: JU259. MAPPING OF ANTIBODY-BINDING EPITOPES OF A RECOMBINANT POA-P-IX ALLERGEN. ZHANG L; OLSEN E; KISIL F T; HILL R D; SEHON A H; MOHAPATRA S S (Reprint). UNIV MANITOBA, DEPT IMMUNOL, WINNIPEG R3E 0W3, MANITOBA, CANADA; UNIV MANITOBA, MRC, ALLERGY RES GRP, WINNIPEG R3E 0W3, MANITOBA, CANADA. MOLECULAR IMMUNOLOGY (NOV 1992) Vol. 29, No. 11, pp. 1383-1389. ISSN: 0161-5890. Pub. country: CANADA. Language: ENGLISH.
*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB Antibody binding epitopes of a recombinant Poa p IX allergen were delineated using recombinant DNA and solid-phase peptide synthesis procedures. The full-length cDNA clone KBG60 and its four overlapping recombinant fragments, KBG60.1, KBG60.2, KBG8.3 and KBG10 which spanned the entire molecule were synthesized in E. coli with aid of the plasmid expression vector, pWR590.1. The antigenic and allergenic sites of these recombinant proteins were analyzed by ELISA using human **IgE** and murine IgG antibodies, It was thus demonstrated that although the epitopes were found on all the fragments tested, the majority of these were located on a C-terminal fragment, rKBG8.3. Furthermore, synthetic peptides were also employed to identify the epitopes of rKBG60 protein. The use of antisera raised against native KBG pollen extract and the recombinant KBG8.3 protein to scan a total of 56 overlapping deca-penta peptides, covering the entire rKBG60 protein, revealed that 10 positive peptides involved in the antibody-binding site(s). Taken together, the results of these studies indicate that rKBG60 protein possesses at least 10 antibody binding epitopes.

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L17 ANSWER 1 OF 31 MEDLINE DUPLICATE 1
2002300838 Document Number: 22035325. PubMed ID: 11967231. Generation of therapeutic antibody responses against **IgE** through vaccination. Vernersson Molly; Ledin Anna; Johansson Jeannette; **Hellman Lars**. (Department of Cell and Molecular Biology, Biomedical Center, University of Uppsala, S-751 24 Uppsala, Sweden. ) FASEB JOURNAL, (2002 Jun) 16 (8) 875-7. Journal code: 8804484. ISSN: 1530-6860. Pub. country: United States. Language: English.
AB **IgE** is the central mediator in atopic allergies such as hay fever, eczema, and asthma; therefore, it is a prime target in the development of allergen-independent preventive treatments. We describe an active immunization strategy that has the potential to reduce **IgE**

to a clinically significant extent. The active vaccine component is a chimeric **IgE** molecule, Cepsilon2-Cepsilon3-Cepsilon4. The receptor-binding target domain, Cepsilon3, is derived from the recipient species, whereas the flanking domains, Cepsilon2 and Cepsilon4, are derived from an evolutionarily distant mammal. The flanking domains have dual functions, acting both as structural support for the Cepsilon3 domain and to break T cell tolerance by providing foreign T cell epitopes. The efficacy of the vaccine was studied in an ovalbumin-sensitized rat model. Vaccination resulted in antibody responses against **IgE** in all rats and in a substantial reduction in serum **IgE** levels in three out of four strains. The skin reactivity upon allergen challenge was significantly reduced in vaccinated animals. The vaccine appears to be safe to use as an antigen. No cross-linking activity was observed in sera of vaccinated animals, and the response to vaccination was reversible with time. Our results suggest that active immunization against **IgE** has the potential to become a therapeutic method for humans.

L17 ANSWER 2 OF 31 SCISEARCH COPYRIGHT 2002 ISI (R)

2002:395291 The Genuine Article (R) Number: 549CA. Generation of therapeutic antibody responses against **IgE** through vaccination. Vernersson M; Ledin A; Johansson J; **Hellman L (Reprint)**. Uppsala Univ, Ctr Biomed, Dept Cell & Mol Biol, Box 596, S-75124 Uppsala, Sweden (Reprint); Uppsala Univ, Ctr Biomed, Dept Cell & Mol Biol, S-75124 Uppsala, Sweden; Resistentia Pharmaceut AB, S-75323 Uppsala, Sweden. FASEB JOURNAL (APR 2002) Vol. 16, No. 6, pp. U104-U124. Publisher: FEDERATION AMER SOC EXP BIOL. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA. ISSN: 0892-6638. Pub. country: Sweden. Language: English.

*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB **IgE** is the central mediator in atopic allergies such as hay fever, eczema, and asthma; therefore, it is a prime target in the development of allergen-independent preventive treatments. We describe an active immunization strategy that has the potential to reduce **IgE** to a clinically significant extent. The active vaccine component is a chimeric **IgE** molecule, Cepsilon2-Cepsilon3-Cepsilon4. The receptor-binding target domain, Cepsilon3, is derived from the recipient species, whereas the flanking domains, Cepsilon2 and Cepsilon4, are derived from an evolutionarily distant mammal. The flanking domains have dual functions, acting both as structural support for the Cepsilon3 domain and to break T cell tolerance by providing foreign T cell epitopes. The efficacy of the vaccine was studied in an ovalbumin-sensitized rat model. Vaccination resulted in antibody responses against **IgE** in all rats and in a substantial reduction in serum **IgE** levels in three out of four strains. The skin reactivity upon allergen challenge was significantly reduced in vaccinated animals. The vaccine appears to be safe to use as an antigen. No cross-linking activity was observed in sera of vaccinated animals, and the response to vaccination was reversible with time. Our results suggest that active immunization against **IgE** has the potential to become a therapeutic method for humans.

L17 ANSWER 3 OF 31 CAPLUS COPYRIGHT 2002 ACS

2000:314492 Document No. 132:346610 Enhanced vaccines. **Hellman, Lars T.** (Resistentia Pharmaceuticals AB, Swed.). PCT Int. Appl. WO 2000025722 A2 20000511, 50 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-SE1896 19991021. PRIORITY: US 1998-PV106652 19981102; US 1999-401636 19990922.

AB The invention relates to methods and materials involved in the treatment

and prevention of various diseases such as infections and **IgE** -related diseases. Specifically, the invention relates to methods and materials that can be used to vaccinate a mammal against specific self or non-self antigens. For example, the methods and materials described herein can be used to reduce the effects of **IgE** antibodies within a mammal by reducing the amt. of total and receptor bound **IgE** antibodies in the mammal. In addn., the invention provides vaccine conjugates, immunogenic polypeptides, nucleic acid mols. that encode immunogenic polypeptides, host cells contg. the nucleic acid mols. that encode immunogenic polypeptides, and methods for making vaccine conjugates and immunogenic polypeptides as well as nucleic acid mols. that encode immunogenic polypeptides. Further, the invention provides an **IgE** vaccine that induces an anti-self **IgE** response in a mammal.

L17 ANSWER 4 OF 31 MEDLINE DUPLICATE 2

2001103120 Document Number: 20545223. PubMed ID: 11093157. Murine mast cell lines as indicators of early events in mast cell and basophil development. Lunderius C; Xiang Z; Nilsson G; **Hellman L.** (Department of Cell and Molecular Biology, Uppsala University, Biomedical Center, Uppsala, Sweden. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (2000 Dec) 30 (12) 3396-402. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB To study early events in mast cell / basophil development, the phenotype of a panel of murine cell lines at various stages of differentiation was determined. Based on the expression on various mast cell-specific proteases and several additional hematopoietic differentiation markers, the cell lines CFTL-15 and MCP5 / L were clearly identified as mast cells, although with a relatively immature phenotype. These two cell lines express the high-affinity **IgE** receptor alpha-chain, the mouse mast cell protease (MMCP)-5 and the carboxypeptidase A (CPA). Bone marrow-derived mast cells and the transplantable mast cell tumor MTC were shown to express the **IgE** receptor alpha-chain, MMCP-5 and CPA, as well as the mast cell tryptase MMCP-6 and the chymase MMCP-4, a protease expressed only during late stages of mast cell differentiation. These two cell types thus display a more mature mast cell phenotype. In contrast, the cell lines P815 and 32D cl3 did not express any mast cell differentiation markers. Interestingly, the IC-2 cell line was shown to express several markers for immature mast cells and in addition MMCP-8, a serine protease which may represent a marker for mouse basophils. By antibody staining, almost all IC-2 cells were shown to express MMCP-8. This indicates that individual cells may simultaneously express both mast cell and basophil markers. Moreover, these findings suggest that an early branch point in hematopoietic development where mast cells and basophils have a common precursor cell may exist.

L17 ANSWER 5 OF 31 MEDLINE DUPLICATE 3

2000452719 Document Number: 20462624. PubMed ID: 11009100. MMCP-8, the first lineage-specific differentiation marker for mouse basophils. Elevated numbers of potent IL-4-producing and MMCP-8-positive cells in spleens of malaria-infected mice. Poorafshar M; Helmby H; Troye-Blomberg M; **Hellman L.** (Department of Cell and Molecular Biology, University of Uppsala, Sweden. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (2000 Sep) 30 (9) 2660-8. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB In mice infected with the non-lethal malaria parasite Plasmodium chabaudi chabaudi AS, a prominent switch from a Th1 to a Th2 type of response occurs in CD4+ T cells at the time of peak parasitemia or shortly thereafter (9-15 days after infection). This is accompanied by a major increase in IL-4, and a similar decrease in IFN-gamma-producing cells. Non-B-non-T cells have been shown to be the main source of the IL-4 in these mice. The IL-4-producing cells are hyperresponsive to IL-3, indicating mast cell or basophil origin. To further characterize this cell

population we have studied various organs at different time points of malarial infection by Northern blot analysis. No significant increase in the expression of any of the classical mouse mast cell serine proteases (MMCP)-1 to 7 or carboxypeptidase A was detected in the spleen during the entire infection. However, a marked increase in the expression of MMCP-8 was observed in the spleen at around day 15 post infection. Isolation of **IgE** receptor-positive cells from spleen shortly after peak parasitemia led to a prominent enrichment of MMCP-8-expressing cells. Fifty thousand of these cells were, after IL-3 stimulation, found to produce IL-4 to levels comparable with more than one million fully activated T cells. Our results show that basophil-like cells are very potent producers of IL-4 and that IL-4 produced by these cells may be of major importance for the initiation of a Th2 response. In addition, the detection of MMCP-8 in these cells has led to the identification of the first basophil-specific differentiation marker in the mouse.

L17 ANSWER 6 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2000:377491 Document No.: PREV200000377491. The evolution of modern post switch isotypes; A study of immunoglobulin isotypes in marsupials and monotremes. Aveskogh, M. (1); Vernersson, M. (1); **Hellman, L. (1)** ; Munday, B.. (1) Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala Sweden. Developmental & Comparative Immunology, (2000) Vol. 24, No. Supplement 1, pp. S9. print. Meeting Info.: 8th Congress of the International Society of Developmental and Comparative Immunology Cairns, Australia July 03-06, 2000 ISSN: 0145-305X. Language: English. Summary Language: English.

L17 ANSWER 7 OF 31 MEDLINE DUPLICATE 4
2000043989 Document Number: 20043989. PubMed ID: 10579388. Cloning and structural analysis of IgM (mu chain) and the heavy chain V region repertoire in the marsupial Monodelphis domestica. Aveskogh M; Pilstrom L; **Hellman L.** (Department of Cell and Molecular Biology, University of Uppsala, Biomedical Center, Sweden. ) DEVELOPMENTAL AND COMPARATIVE IMMUNOLOGY, (1999 Oct-Dec) 23 (7-8) 597-606. Journal code: 7708205. ISSN: 0145-305X. Pub. country: United States. Language: English.
AB To address the question of the Ig isotype repertoire of non placental mammals, we have examined the Ig expression in the marsupial Monodelphis domestica (grey short tailed opossum). Screening of an opossum spleen cDNA library has previously led to the isolation of full length clones for opossum IgG (gamma chain), **IgE** (epsilon chain) and IgA (alpha chain). We now present the isolation of several cDNA clones encoding the entire constant regions of the opossum IgM (mu chain). A comparative analysis of the amino acid sequences for IgM from various animal species showed that opossum IgM, within the various animals studied, is the most divergent member of its Ig class. However, it still conforms to the general structure of IgM in other vertebrates. Four Ig classes have now been identified in opossum and only one isotype is apparently present within each Ig class, IgM, IgG, IgA and **IgE**. Opossum has previously been shown to have a limited VH region diversity, with only two V gene families. Both of these belong to the group III of mammalian VH sequences. This limitation in variability is to some extent compensated for by a large variation in D, P and N regions, both in size and in sequence. However, evidence for the expression of only two functional J segments has so far been detected, which indicates a rather limited diversity also of the J segments in the opossum.

L17 ANSWER 8 OF 31 CAPLUS COPYRIGHT 2002 ACS
1999:56260 Document No. 130:266025 Vaccines against allergies. **Hellman, L.** (Department of Medical Immunology and Microbiology, BMC, Uppsala, S-751 23, Swed.). Handbook of Experimental Pharmacology, 133(Vaccines), 499-526 (English) 1999. CODEN: HEPHD2. ISSN: 0171-2004. Publisher: Springer-Verlag.
AB A review with 135 refs. A detailed description of allergic immune

response along with a discussion of some of the currently available immunotherapies is presented. Application of modified allergens, oral administration of allergens and allergen exts., peptide vaccines, cytokine agonists and antagonists as immunotherapeutic approach is discussed. In addn., use of low mol. wt. substances that interfere with the interactions between **IgE** and its receptors as well as strategies involving the depletion of plasma and mast cell bound **IgE** by treatment with monoclonal anti-**IgE** antibodies is also mentioned. Finally, strategies involving induction of strong anti-**IgE** response by vaccination are outlined.

L17 ANSWER 9 OF 31 MEDLINE DUPLICATE 5
1998425532 Document Number: 98425532. PubMed ID: 9754561. Evidence for an early appearance of modern post-switch isotypes in mammalian evolution; cloning of **IgE**, IgG and IgA from the marsupial Monodelphis domestica. Aveskogh M; **Hellman L**. (Department of Medical Biochemistry and Microbiology, University of Uppsala, Sweden. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (1998 Sep) 28 (9) 2738-50. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB In birds, reptiles and amphibians the IgY isotype exhibits the functional characteristics of both of IgG and **IgE**. Hence, the gene for IgY most likely duplicated some time during early mammalian evolution and formed the ancestor of present day IgG and **IgE**. To address the question of when IgY duplicated and formed two functionally distinct isotypes, and to study when IgG and IgA lost their second constant domains, we have examined the Ig expression in a non-placental mammal, the marsupial Monodelphis domestica (grey short-tailed opossum). Screening of an opossum spleen cDNA library revealed the presence of all three isotypes in marsupials. cDNA clones encoding the entire constant regions of opossum **IgE** (epsilon chain), IgG (gamma chain) and IgA (alpha chain) were isolated, and their nucleotide sequences were determined. A comparative analysis of the amino acid sequences for IgY, IgA, **IgE** and IgG from various animal species showed that opossum **IgE**, IgG and IgA on the phylogenetic tree form branches clearly separated from their eutherian counterparts. However, they still conform to the general structure found in eutherian **IgE**, IgG and IgA. Our findings indicate that all the major evolutionary changes in the Ig isotype repertoire, and in basic Ig structure that have occurred since the evolutionary separation of mammals from the early reptile lineages, occurred prior to the evolutionary separation of marsupials and placental mammals.

L17 ANSWER 10 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2002:81032 Document No.: PREV200200081032. Vaccine comprising part of constant region of **IgE** for treatment of **IgE**-mediated allergic reactions. **Hellman, L. T.**. Vaderkvarnsgatan 11A, S-753 29 Uppsala Sweden. Patent Info.: US 5653980 Aug. 5, 1997. Official Gazette of the United States Patent and Trademark Office Patents, (Aug. 5, 1997) Vol. 1201, No. 1, pp. 362. ISSN: 0098-1133. Language: English.

L17 ANSWER 11 OF 31 MEDLINE DUPLICATE 6
1998025077 Document Number: 98025077. PubMed ID: 9321425. Cloning, structural analysis, and expression of the pig **IgE** epsilon chain. Vernersson M; Pejler G; Kristersson T; Alving K; **Hellman L** . (Department of Medical Immunology and Microbiology, University of Uppsala, Sweden. ) IMMUNOGENETICS, (1997) 46 (6) 461-8. Journal code: 0420404. ISSN: 0093-7711. Pub. country: United States. Language: English.

AB As a step in the evolutionary studies of immunoglobulin E (**IgE**) and for the purpose of developing new reagents that will facilitate a more detailed analysis of **IgE**-mediated inflammatory reactions in a large animal model, we here present the cloning of the epsilon chain of **IgE** in the domestic pig (Sus scrufa). A partial cDNA clone for the

epsilon chain of pig **IgE** was isolated by polymerase chain reaction (PCR) amplification using degenerate primers directed against conserved regions in the second (CH2) and the fourth (CH4) constant domains of **IgE**. cDNA derived from mRNA isolated from the spleen and lymph nodes of a pig actively sensitized with a protein extract from the nematode Ascaris suum was used as template. Screening of a spleen cDNA library with the partial cDNA clone as probe resulted in isolation of a clone that contained the entire coding region. The nucleotide sequence was determined and was found to conform with the previously identified mammalian epsilon-chain sequences. The highest degree of similarity was found to sheep **IgE**. A DNA construct encoding a baculovirus signal sequence, a histidine hexapeptide, and the CH2-CH3-CH4 domains of the pig **IgE** epsilon chain was obtained by PCR amplification. The construct was ligated into the baculovirus expression vector pVL1392. Infection of High Five insect cells with recombinant baculovirus resulted in expression and secretion of a soluble 6 x His-CH2-CH3-CH4 protein product.

L17 ANSWER 12 OF 31 MEDLINE DUPLICATE 7
97249376 Document Number: 97249376. PubMed ID: 9095262. Is vaccination against **IgE** possible?. **Hellman L.** (Department of Medical Immunology and Microbiology, University of Uppsala. ) ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1996) 409 337-42. Ref: 18. Journal code: 0121103. ISSN: 0065-2598. Pub. country: United States. Language: English.

AB A substantial reduction in the levels of both total and antigen specific **IgE** will most likely result in improved symptom scores in atopic individuals. Based on this assumption we initiated a project to study the possibility of reducing levels of circulating and mast cell bound **IgE**, by inducing a strong autoimmune antibody response against **IgE** in the host. Bacterially produced fusion proteins containing constant domains two (CH2) and three (CH3) of rat **IgE** directly linked to the glutathione-S-transferase (GST) protein from Schistosoma japonicum or to the maltose binding protein of Esherichia coli were used as the active components of the allergy vaccine. Injection of either of these fusion proteins together with adjuvant led to the induction of a strong autoimmune anti-**IgE** response in several **IgE** low or medium responder strains of rats. Vaccination of ovalbumin sensitised Wistar rats with the GST-C2C3 fusion protein resulted in a profound decrease in serum **IgE** levels and later in a nearly complete block in histamine release from mast cells and basophils upon challenge with either a cross-linking polyclonal anti-**IgE** antiserum or a specific allergen. This shows that it is possible to reduce **IgE** levels in an animal to such an extent that it gives a clear clinical effect. Recent studies with an extended panel of rat strains including four **IgE** high responder strains, indicate that induction of the autoimmune response is dependent on the plasma concentration of **IgE** before vaccination. A high concentration of **IgE** has a negative effect on the induction of autoimmunity, most likely by inducing a B-cell tolerance in the host. Vaccinated subjects with very high **IgE** concentrations thereby responds poorly to the vaccine. Current studies are aimed at overcoming this potential limitation of the vaccination procedure.

L17 ANSWER 13 OF 31 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 8
96297255 EMBASE Document No.: 1996297255. Allergy vaccines: A review of developments. **Hellman L.**; Carlsson M.. Department of Medical Immunology, Biomedical Centre, University of Uppsala,S-751 23 Uppsala, Sweden. Clinical Immunotherapeutics 6/2 (130-142) 1996. ISSN: 1172-7039. CODEN: CIMMEA. Pub. Country: New Zealand. Language: English. Summary Language: English.

AB Immunotherapy by vaccination (hyposensitisation) has been used since the beginning of this century for the treatment of atopic diseases.

Immunotherapy is still widely used and in the hands of specialists is quite safe. However, the use of crude allergen extracts, doubts about its efficacy for many allergens and the risk of severe adverse effects when not properly administered have raised questions about the place of hyposensitisation as part of modern immunotherapy. The relatively efficient pharmacotherapy of allergic diseases has also reduced the need for traditional high dose immunotherapy. However, progress in the understanding of the basic immune mechanisms of allergy and in the characterisation of dominant allergens has stimulated the development of several novel strategies for immunotherapy. A few of these have the potential of reaching the clinic in the near future. The most promising areas of this rapidly developing field will be covered in this article. The 4 main areas which will be discussed in more detail are: (i) progress in the area of modifications :of allergen extracts or purified recombinant allergens by allergen cross-linking, monomethoxy-polyethylene glycol coupling or immune complex formation, with the aim of reducing the allergenicity of the antigen or to tolerise or redirect the immune response to a mainly T helper 1 response; (ii) oral administration of allergens or allergen extracts, possibly by using bacteria as live vaccines; (iii) treatment with immunodominant peptides from major allergens, with the aim of inducing unresponsiveness in allergen-specific T cells; and (iv) immune intervention directly targeting the **IgE** molecule, to deplete circulating and mast cell bound **IgE**, by treatment with monoclonal antibodies or by vaccination against **IgE** using parts of the **IgE** molecule covalently coupled to a foreign carrier protein.

L17 ANSWER 14 OF 31 MEDLINE DUPLICATE 9
96285637 Document Number: 96285637. PubMed ID: 8693292. Characterization of a human basophil-like cell line (LAMA-84). Blom T; Nilsson G; Sundstrom C; Nilsson K; **Hellman L.** (Department of Medical Immunology, University of Uppsala, Sweden. ) SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (1996 Jul) 44 (1) 54-61. Journal code: 0323767. ISSN: 0300-9475. Pub. country: ENGLAND: United Kingdom. Language: English.

AB LAMA-84, a human leucocytic cell line, which upon establishment was described as having megakaryocytic, erythroid and granulocytic characteristics, was analysed for expression of various differentiation markers. In addition to some of the previously described phenotypic characteristics, this cell line was found to express mRNA for several proteins characteristic for basophilic leucocytes and mast cells. The authors show that LAMA-84 cells express mRNA for the mast cell tryptase, the proteoglycan core protein, carboxypeptidase A and the alpha and beta chains of the high affinity **IgE** receptor (Fc epsilon RI). The authors examined the potential of LAMA-84 to differentiate in serum-free medium or after DMSO or PMA treatment. Depending on the inducing factor, surface expression of the Fc epsilon RI alpha-chain was increased from 20% to 35-50% of the cells and mRNA levels for tryptase were increased in serum-free medium and after DMSO treatment. LAMA-84 was found to express CD13, CDw17, CD29, CD33, CD40, CD45 and CD117. Furthermore, mRNA for the eosinophil/basophil markers Charcot-Leyden crystal (CLC) protein and the major basic protein (MBP), as well as the erythrocyte differentiation marker alpha-globin, was detected. However, the authors observed only trace amounts of mRNA for another erythroid differentiation marker (glycophorin), trace amounts of the megakaryocytic marker GPIIIa, and no detectable level of GPIb alpha. By comparing the expression pattern of a panel of differentiation markers in LAMA-84, and a second human cell line (KU812) expressing a basophil phenotype, it is evident that these cell lines, which presently are the only two cell lines identified with basophilic characteristics, share a large number of phenotypic characteristics.

L17 ANSWER 15 OF 31 MEDLINE DUPLICATE 10
96062118 Document Number: 96062118. PubMed ID: 7481558. A single major

transcript encodes the membrane-bound form of rat immunoglobulin E. Aveskogh M; **Hellman L.** (Department of Medical Immunology and Microbiology, University of Uppsala, Sweden. ) SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (1995 Nov) 42 (5) 535-9. Journal code: 0323767. ISSN: 0300-9475. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The primary structure of the membrane-bound form of rat immunoglobulin E was determined by PCR amplification and nucleotide sequence analysis of its mRNA. The sequence was found to correspond to the previously identified membrane exons of the rat epsilon chain gene. The donor splice site in the C4 exon was mapped to a position 35 nt upstream of the stop codon for the secreted form of rat **IgE**. Therefore, the membrane-bound **IgE** lacks the 12 C-terminal amino acids present in the secreted form of the protein. Recently, five novel epsilon chain transcripts were isolated from human **IgE** producing B-cells or B-cell lines. Four of these transcripts encode proteins which differ in their C-terminal ends from the classical membrane or secreted forms of human **IgE**. To investigate if these transcripts were likely to represent functional mRNAs, their evolutionary conservation was studied by screening a rat **IgE** producing B-cell line for the expression of similar transcripts. By PCR amplification and cloning of transcripts, containing both the C3 and the M2 exons, approximately 10,000 independent cDNA clones were obtained. These clones were screened with probes directed against regions specific for each of the five novel human epsilon chain mRNAs. However, no evidence was found for the presence of transcripts with a similar structure, indicating that no specific function associated with these transcripts and their corresponding proteins has been conserved between human and rat. The lack of additional M2-containing transcripts in the rat suggest that the novel human **IgE** transcripts are byproducts of differential splicing and that they most likely encode proteins with no evolutionarily important function.

L17 ANSWER 16 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

1995:383188 Document No.: PREV199598397488. Analysis of a novel allergy vaccine designed for the treatment of **IgE**-mediated allergies. **Hellman, L.**; Carlsson, M.; Aveskogh, M.; Akerlund, R.. Dep. Med. Immunol. Microbiol., Uppsala Univ., Uppsala Sweden. 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY.. (1995) pp. 437. The 9th International Congress of Immunology. Publisher: 9th International Congress of Immunology San Francisco, California, USA. Meeting Info.: Meeting Sponsored by the American Association of Immunologists and the International Union of Immunological Societies San Francisco, California, USA July 23-29, 1995 Language: English.

L17 ANSWER 17 OF 31 MEDLINE DUPLICATE 11

94248689 Document Number: 94248689. PubMed ID: 8191224. Phenotypic characterization of the human mast-cell line HMC-1. Nilsson G; Blom T; Kusche-Gullberg M; Kjellen L; Butterfield J H; Sundstrom C; Nilsson K; **Hellman L.** (Department of Pathology, University of Uppsala, Sweden. ) SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (1994 May) 39 (5) 489-98. Journal code: 0323767. ISSN: 0300-9475. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The cell line HMC-1, derived from a patient with mast cell leukaemia, is the only established cell line exhibiting a phenotype similar to that of human mast cells. This paper reports on a detailed characterization of the expression of a panel of markers for various types of immature and mature haematopoietic cells in the HMC-1. We also studied the potential of HMC-1 to differentiate upon treatment with conditioned media from the human T-cell line Mo, retinoic acid or DMSO. HMC-1 was found to express several mast cell-related markers. A high expression of Kit, the receptor for stem-cell factor, was detected. The majority of the cells were stained with a MoAb against the mast cell-specific serine protease tryptase. Of particular interest was the finding that beta-tryptase mRNA, but not alpha-tryptase mRNA, was expressed in HMC-1. Using enzyme-histochemistry

we were able to show that the beta-tryptase was enzymatically active, indicating that tryptase can form active homotetramers. Both heparin and chondroitin sulfate were found to be present in approximately equal amounts. HMC-1 lacked surface expression of the high-affinity **IgE** receptor, which was confirmed by the absence of mRNA of the alpha- and beta-chains of the **IgE**-receptor complex. However, a strong expression of the gamma-chain of the **IgE**-receptor complex was detected. A positive staining of the monocyte/macrophage marker CD68 was obtained, as well as a strong hybridization signal for the eosinophilic/basophilic-related differentiation marker the Charcot-Leyden crystal. Treatment of HMC-1 with conditioned media from the human T-cell line Mo, retinoic acid or DMSO induced only moderate changes in the surface or intracellular expression of the studied markers. The agents tested neither induced any of the monocyte/granulocyte markers examined, nor expression of the Fc epsilon RI alpha-chain.

L17 ANSWER 18 OF 31 MEDLINE DUPLICATE 12
94130960 Document Number: 94130960. PubMed ID: 8299691. Profound reduction in allergen sensitivity following treatment with a novel allergy vaccine. **Hellman L.** (Department of Immunology, University of Uppsal, Sweden. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (1994 Feb) 24 (2) 415-20. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB A novel approach is described for the treatment of **IgE**-mediated allergic reactions which is based on the induction of a strong anti-**IgE** response in the host. Vaccination of ovalbumin-sensitized rats with constant domains two and three of rat **IgE** coupled to a heterologous carrier protein resulted in a profound decrease in serum levels of **IgE**, and later in a nearly complete block of histamine release from mast cells and basophils upon challenge with either a cross-linking polyclonal anti-**IgE** antiserum or a specific allergen.

L17 ANSWER 19 OF 31 CAPLUS COPYRIGHT 2002 ACS
1993:219841 Document No. 118:219841 Vaccine comprising part of constant region of **IgE** for treatment of **IgE**-mediated allergic reactions. **Hellman, Lars T.** (Swed.). PCT Int. Appl. WO 9305810 A1 19930401, 27 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, US; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1992-SE673 19920925. PRIORITY: SE 1991-2808 19910926.

AB A vaccine for alleviating the symptoms of or preventing the induction of **IgE**-mediated allergic reactions in a mammal contains a protein having the entire amino acid sequence of the const. CH2CH3 domains of the .epsilon. chain of **IgE** mol. from the mammal species or a structurally stable subunit of said amino acid sequence contg. .gtoreq.12 amino acids, in its original or in a mutated or multimerized form, and optionally contg. an adjuvant. The cDNA sequence for CH2CH3 regions of the rat .epsilon. chain of **IgE** was cloned and ligated into a com. available vector for the prodn. of a fusion protein (purity of .apprx.50%) in Escherichia coli. Strong immune response was obtained when rats were injected s.c. with 100.mu.g of fusion protein in 0.2mL admixt. with an adjuvant.

L17 ANSWER 20 OF 31 MEDLINE DUPLICATE 13
93122085 Document Number: 93122085. PubMed ID: 8419166. Characterization of four novel epsilon chain mRNA and a comparative analysis of genes for immunoglobulin E in rodents and man. **Hellman L.** (Department of Immunology, University of Uppsala, Sweden. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (1993 Jan) 23 (1) 159-67. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language:

English.

AB The nucleotide sequence of the 3' region of the epsilon chain gene for human **IgE** is presented. A comparison of the entire region from 5' of exon C1 to the M2 exon of the mouse, rat and human epsilon chain genes shows that the overall structure of the epsilon chain gene have changed only minimally during the 60-70 million years of evolutionary separation between rodents and man. We have previously shown that a number of rearrangements larger than 10 bp have relatively recently occurred in the C4/M1 intron of the rat or the mouse epsilon chain genes. A majority of these rearrangements were found within or in close proximity to repetitive sequences of Z-DNA-forming potential (CA dinucleotide repeats). The C4/M1 intron has evolved very rapidly, to such an extent that no apparent homology can be detected between rodents and man. Only remnants of the repetitive sequences are present in man, supporting the theory that repetitive sequences having Z-DNA-forming properties may play a role in the evolution of the eucaryote genome by promoting recombinations, leading to a rapid evolutionary drift of sequences in close proximity to these repeats. We report here the characterization of the membrane domains of human **IgE** and four novel mRNA transcribed from the human epsilon chain locus. The primary structures have been determined by polymerase chain reaction cloning and nucleotide sequence analysis. All five mRNA contain the C3 domain and the membrane exon 2 (M2). Due to frame shifts caused by novel splice sites or novel splice-site combinations, the proteins encoded by three out of these four novel mRNA differ in their carboxy-terminal end from the classical secreted or membrane-bound immunoglobulins. Northern blot analysis shows significant levels of at least three out of these four novel mRNA in an **IgE**-producing human cell line. One of the mRNA encodes a transmembrane-like structure which has characters in common with the transmembrane region of the CD3 components of the T cell receptor complex (CD3 gamma, delta and epsilon). This indicates that **IgE**-producing B cells possibly have two separate signal-transducing systems. A comparison of the classical membrane anchoring domain of the human & chain with a panel of immunoglobulin membrane domains from fish to higher mammals is presented. A tyrosine and a glutamine residue is found to be conserved between all cytoplasmic domains of all post-switch immunoglobulin classes indicating a functional conservation of these amino acid residues.(ABSTRACT TRUNCATED AT 400 WORDS)

L17 ANSWER 21 OF 31 MEDLINE DUPLICATE 14

92347396 Document Number: 92347396. PubMed ID: 1639103. Phenotypic characterization of KU812, a cell line identified as an immature human basophilic leukocyte. Blom T; Huang R; Aveskogh M; Nilsson K; **Hellman L**. (Department of Immunology, University of Uppsala, Sweden. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (1992 Aug) 22 (8) 2025-32. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB The knowledge about the differentiation of basophilic leukocytes is fragmentary. This report discusses a detailed phenotypic characterization of molecular markers for hematopoietic differentiation in a basophilic leukemia cell line, KU812. The expression of markers for lymphoid, erythroid, neutrophil, eosinophil, monocytic, megakaryocytic, mast cell and basophil differentiation was analyzed at the mRNA level by Northern blots in the KU812 cells, and for reference, in a panel of human cell lines representative of the different hematopoietic differentiation lineages. KU812 was found to express a number of mast cell and basophil-related proteins, i.e. mast cell tryptase, mast cell carboxypeptidase A, high-affinity immunoglobulin (**IgE**) receptor alpha and gamma chains and the core protein for heparin and chondroitin sulphate synthesis. We found no expression of a number of monocyte/-macrophage or neutrophil leukocyte markers except for lysozyme. From earlier studies, it has been shown that lysozyme is not expressed in murine mucosal mast cell lines. This finding, together with the expression

of the mast cell carboxypeptidase in KU812 might distinguish the phenotype of this cell line from that typical of mucosal mast cell lines in rodents. We found a low level of expression of the eosinophil and basophil marker, major basic protein, which might indicate a relationship between basophils and eosinophils. No expression is, however, detected with the eosinophil-specific markers eosinophil cationic protein, eosinophil-derived neurotoxin or eosinophil peroxidase. We also report an extensive screening for inducers of basophilic differentiation of the KU812 cells. The most efficient protocol of induction included serum starvation which led to a dramatic increase in a number of markers specific for mast cells and basophils such as tryptase, carboxypeptidase A and the heparin core protein. Finally, diisopropylfluorophosphate analysis of total protein extracts from KU812 show four labeled protein bands with sodium dodecyl sulfate-polyacrylamide gel electrophoresis, indicating that this cell line expresses at least three previously undescribed serine proteases of which one or more could be a potential basophil-specific marker(s).

L17 ANSWER 22 OF 31 MEDLINE DUPLICATE 15

92086826 Document Number: 92086826. PubMed ID: 1749921. Enhancement of **IgE** synthesis in the human myeloma cell line U-266 with an **IgE** binding factor from a human T-cell line. Nilsson G; Jernberg H; **Hellman L**; Ahlstedt S; Nilsson K. (Department of Immunology, Uppsala University, Sweden. ) SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (1991 Dec) 34 (6) 721-6. Journal code: 0323767. ISSN: 0300-9475. Pub. country: ENGLAND: United Kingdom. Language: English.

AB An **IgE**-binding factor(s) (**IgE**-BF(s] was partially purified from the supernatant of human HTLV-II carrying T-cell line MO. This **IgE**-BF(s) was shown to increase the **IgE** synthesis in the human myeloma cell line U-266, but did not affect its viability or growth. The effect of the **IgE**-BF(s) was dose-dependent and selective for **IgE** protein synthesis as beta 2-microglobulin synthesis in the U-266 and the immunoglobulin production in the U-1958 IgG-secreting human myeloma cell line were unaffected. The **IgE** -BF(s) increased the production of the epsilon heavy chain but not the lambda light chain production. The **IgE**-BF(s) was distinct from IL-1 beta, IL-3, IL-4, IL-5, IL-6, TNF-alpha, IFN-alpha, -beta, -gamma, M-CSF, and fragments of CD23.

L17 ANSWER 23 OF 31 MEDLINE DUPLICATE 16

88255082 Document Number: 88255082. PubMed ID: 3133230. Immunoglobulin synthesis in the human myeloma cell line U-266; expression of two immunoglobulin heavy chain isotypes (epsilon and alpha) after long-term cultivation in vitro. **Hellman L**; Josephson S; Jernberg H; Nilsson K; Pettersson U. (Department of Medical Genetics and Microbiology, Biomedical Center, Uppsala, Sweden. ) EUROPEAN JOURNAL OF IMMUNOLOGY, (1988 Jun) 18 (6) 905-10. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB A human **IgE**-producing myeloma has been cultivated in vitro as a continuous cell line (U-266) since 1968. Analysis of immunoglobulin production during early passages of the cell line demonstrated a high synthesis rate of monoclonal **IgE**. Analysis of late passages, cultivated after 1980, revealed a 3-6-fold lower rate of **IgE** secretion. This decrease was accompanied by the appearance of small amounts of IgA in the culture medium together with **IgE**. RNA was extracted from a late passage of U-266 and analyzed by Northern blotting, using epsilon and alpha-specific oligonucleotides as hybridization probes. The results showed the presence of epsilon as well as alpha-specific mRNA. Moreover the results demonstrated that the latter mRNA was derived from the alpha 2 locus and that the epsilon and the alpha 2-specific mRNA contained the same V region sequences. Southern blot analysis of DNA from the late passage of the U-266 cell line failed to reveal a recombinatory switch from the epsilon locus to the alpha 2 locus. The expression of

alpha 2 is thus likely to be caused by differential splicing rather than by an isotype switch at the DNA level.

L17 ANSWER 24 OF 31 CAPLUS COPYRIGHT 2002 ACS
1988:584687 Document No. 109:184687 A rapidly evolving region in the immunoglobulin heavy chain loci of rat and mouse: postulated role of (dC-dA)n.cntdot.(dG-dT)n sequences. **Hellman, Lars**; Steen, Marie Louise; Sundvall, Mats; Pettersson, Ulf (Biomed. Cent., Univ. Uppsala, Uppsala, S-751 23, Swed.). Gene, 68(1), 93-100 (English) 1988. CODEN: GENED6. ISSN: 0378-1119.
AB The nucleotide sequences of the introns that are located between the C4 exon and the first membrane exon of mouse and rat Ig .epsilon.-chain genes were detd. The rat intron sequence contains 4 sep. clusters of repetitive sequences, all of which consisted of (dC-dA)n.cntdot.(dG-dT)n dinucleotide repeats. A comparison between this chromosomal region in mouse and rat revealed 4 deletions or duplications, three of which have occurred inside or at the borders of the CA clusters. Rearrangements have occurred inside or at the borders of all 4 repeats after the evolutionary sepn. of mouse and rat. The sequence comparisons reveals in addn. a duplication, connected to the CA repeats, which has occurred early in evolution, before the evolutionary divergence of mouse and rat. These findings suggest that (dC-dA)n.cntdot.(dG-dT)n sequences are potential targets for recombination events.

L17 ANSWER 25 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 17
1988:123473 Document No.: BR34:59335. CHARACTERIZATION OF THE RECEPTOR BINDING PART OF RAT **IGE** TO RBL CELLS BY CONSTRUCTION OF CHIMERIC ANTIBODIES. STEEN M-L; **HELLMAN L**; PETTERSSON U. DEP. MED. GENET., UPPS. UNIV., BOX 589, UPPSALA, SWED.. EIGHTEENTH ANNUAL GENERAL MEETING OF THE SCANDINAVIAN SOCIETY FOR IMMUNOLOGY, UPPSALA, SWEDEN, JUNE 2-4, 1987. SCAND J IMMUNOL. (1987) 26 (3), 330. CODEN: SJIMAX. ISSN: 0300-9475. Language: English.

L17 ANSWER 26 OF 31 SCISEARCH COPYRIGHT 2002 ISI (R)
85:640019 The Genuine Article (R) Number: AUD52. IMMUNOGLOBULIN-E - STRUCTURES AND EXPRESSION - STUDIES ON 3 SPONTANEOUS **IGE** -PRODUCING MYELOMAS. **HELLMAN L (Reprint)**; STEEN M L; PETTERSSON U; ENGSTROM A; KARLSSON J; BENNICH H; JERNBERG H; NILSSON K. UNIV UPPSALA, DEPT MED GENET, S-75105 UPPSALA, SWEDEN; UNIV UPPSALA, DEPT IMMUNOL, S-75105 UPPSALA, SWEDEN; UNIV UPPSALA, DEPT PATHOL, S-75105 UPPSALA, SWEDEN. SCANDINAVIAN JOURNAL OF IMMUNOLOGY (1985) Vol. 22, No. 4, pp. 445. Pub. country: SWEDEN. Language: ENGLISH.

L17 ANSWER 27 OF 31 MEDLINE DUPLICATE 18
86137407 Document Number: 86137407. PubMed ID: 3005118. Nonfunctional immunoglobulin light chain transcripts in two **IgE**-producing rat immunocytomas; implications for the allelic exclusion and transcription activation processes. **Hellman L**; Steen M L; Pettersson U. GENE, (1985) 40 (1) 115-24. Journal code: 7706761. ISSN: 0378-1119. Pub. country: Netherlands. Language: English.
AB The rearrangement and expression of immunoglobulin light-chain genes have been studied in two **IgE**-producing immunocytomas, IR2 and IR162. In the IR2 tumor only one of the kappa-chain alleles is rearranged, expressing a full-length kappa-chain polypeptide. In IR162 one of the kappa-chain alleles is functionally rearranged, expressing a 1200-nucleotide (nt) long mRNA, which encodes a functional 23-kDal kappa-chain polypeptide. The second kappa-chain allele is aberrantly rearranged; i.e., a different V region is connected to a position that is located between the J cluster and the C kappa exon. Two mRNAs which are 750 and 850 nt are transcribed from the aberrantly rearranged allele, both of which appear to encode a 12-kDal polypeptide consisting of a signal sequence that is connected directly to the C region. The levels of

expression from the two kappa-chain alleles are approximately the same, suggesting that no specific mechanism exists to suppress expression of a nonfunctional allele. The rat genome contains a single lambda-chain locus which includes two C-region exons. Although this locus remains in the germ-line configuration in the IR2 and the IR162 tumors, transcripts from the C lambda I and C lambda II regions were detected at a low level in both tumors. These transcripts were detected in RNA from the immunocytomas but not in rat liver RNA indicating that expression is tissue-specific. They lacked V-region sequences and resemble so-called sterile transcripts which are expressed at a low level from unrearranged mu- and kappa-chain genes.

L17 ANSWER 28 OF 31 MEDLINE DUPLICATE 19

86137406 Document Number: 86137406. PubMed ID: 3005117. Structure and expression of kappa-chain genes in two **IgE**-producing rat immunocytomas. **Hellman L**; Engstrom A; Bennich H; Pettersson U. GENE, (1985) 40 (1) 107-14. Journal code: 7706761. ISSN: 0378-1119. Pub. country: Netherlands. Language: English.

AB The light chain expression in two **IgE**-producing rat immunocytomas, IR2 and IR162, was studied. Both immunocytomas produce light chains of the kappa type. The kappa chains were characterized at the protein level by sodium dodecylsulfate (SDS)-polyacrylamide gel electrophoresis (PAGE) and amino acid (aa) sequencing. cDNA clones corresponding to the kappa-chain mRNA were also prepared and sequenced. The results showed that rat kappa chains have the same structure as their mouse counterparts with respect to signal sequence cleavage, somatic mutations in the V-J region and invariance of all the aa positions which are strongly conserved in the frame work regions of mouse V kappa chains (greater than 95% conservation). Results from studies on kappa-chain transcription lend support to the allelic exclusion model with only one functionally expressed light chain in each immunocytoma.

L17 ANSWER 29 OF 31 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 20

1985:232760 Document No.: BA79:12756. RAT IMMUNOGLOBULIN E HEAVY CHAIN LOCUS. STEEN M-L; **HELLMAN L**; PETTERSSON U. DEPARTMENT MEDICAL GENETICS MICROBIOLOGY, UPPSALA UNIVERSITY, BIOMEDICAL CENTRE, BOX 589, S-751 23 UPPSALA, SWEDEN.. J MOL BIOL, (1984) 177 (1), 19-32. CODEN: JMOBAK. ISSN: 0022-2836. Language: English.

AB A 2100 base-pair long sequence was established which covers all 4 constant domains of the rat .epsilon.-chain. An analysis of mRNA from an **IgE** producing rat immunocytoma revealed 2 separate .epsilon.-chain mRNA species, 2.3 .times. 103 and 2.8 .times. 103 base-pairs long. The latter mRNA encodes the membrane binding form of the .epsilon.-chain. The membrane exons which are located .apprx. 2 .times. 103 base-pairs away from the 3'-side of the CH4 exon were also sequenced. A comparison between the rat and mouse .epsilon.-chains at the protein sequence level revealed an overall homology of 80% which, as expected, is considerably higher than the homology found between rat and human .epsilon.-chains. The 4th constant domain together with the 2 membrane exons exhibited the highest degree of homology, 81-89%. Only 2 differences were found when the .epsilon.-chains from LOU and Sprague Dawley rats were compared. The most striking difference at the nucleotide sequence level between the rat, mouse and human .epsilon. genes was found within the 1st intron. The mouse genome contains a unique 366 base-pair long sequence in this region. The inserted sequence is repetitive and present in .apprx. 100 copies in the mouse genome. It is flanked by 22 base-pair long direct repeats and contains also 14 base-pair long inverted repeats, thus having properties in common with transposable elements.

L17 ANSWER 30 OF 31 CAPLUS COPYRIGHT 2002 ACS

1983:28841 Document No. 98:28841 Structure and evolution of the heavy chain from rat immunoglobulin E. **Hellman, Lars**; Pettersson, Ulf;

Engstroem, Aake; Karlsson, Torbjoern; Bennich, Hans (Dep. Med. Genet., Biomed. Cent., Uppsala, S-75123, Swed.). Nucleic Acids Res., 10(19), 6041-9 (English) 1982. CODEN: NARHAD. ISSN: 0305-1048.

AB The nucleotide sequence of the rat .epsilon.-chain mRNA was detd. by sequencing cloned cDNA copies of the mRNA. The established sequence covers the coding region, the 3'-noncoding region, and most of the 5'-noncoding region. A comparison with the nucleotide sequence of the human .epsilon.-chain const. region reveals that C3 and C4 are the most highly conserved domains. The rat .epsilon.-chain contains a C-terminal decapeptide which is not present in the human counterpart.

L17 ANSWER 31 OF 31 MEDLINE DUPLICATE 21

82174576 Document Number: 82174576. PubMed ID: 6803238. Characterization and molecular cloning of the mRNA for the heavy (epsilon) chain of rat immunoglobulin E. **Hellman L**; Pettersson U; Bennich H. PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1982 Feb) 79 (4) 1264-8. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB We report a study of the mRNA for the heavy (epsilon) chain of rat **IgE**. Cytoplasmic RNA was prepared from the two rat immunocytomas IR2 and IR162 and fractionated by sucrose gradient centrifugation. An enriched fraction containing approximately 5% mRNA for the epsilon chain was obtained in this way. When translated in vitro, it produced a 59,000-dalton polypeptide, which in the presence of a membrane fraction yielded a 90,000-dalton polypeptide, presumably through posttranslational modification. Both polypeptides were precipitated by rabbit antisera that were monospecific for rat epsilon chains. The epsilon chain mRNA was estimated to be approximately 2200 nucleotides long and constitutes a minute fraction in the total mRNA both in the IR2 and the IR162 tumors, unlike the mRNA for light chains. Double-stranded cDNA copies prepared frm the RNA fraction, which was enriched for epsilon chain mRNA, were inserted into the Pst I cleavage site of the pBR322 vector. Twenty clones with inserts exceeding 1000 base pairs were used for selection of mRNA from the IR2 tumor. By in vitro translation of the selected mRNA, one clone was identified that yielded a polypeptide with the same size as the unprocessed epsilon chain. The nucleotide sequence was determined for part of the inserted cDNA in this candidate clone and was found to be homologous to a sequence in the constant region (C) of the human epsilon chain. In this communication we report a sequence from the C epsilon 3 domain of the rat **IgE**. When compared to the corresponding sequence of human **IgE**, 55% of the amino acids in the rat sequence were found to be conserved.

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| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
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| FULL ESTIMATED COST | 111.64 | 111.85 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
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| CA SUBSCRIBER PRICE | -6.82 | -6.82 |

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